

AMERICAN JOURNAL OF DIGESTIVE DISEASES AND NUTRITION

The Official Publication of
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

CONTENTS

	Page
SECTION I—CLINICAL MEDICINE	
DIARRHEA— <i>John L. Kantor, M.D.</i>	1
CONSTIPATION— <i>Henry James Spencer, A.M., M.D.</i>	7
THE WELTMANN TEST IN DISEASES OF THE LIVER— <i>Manfred Kraemer, M.D.</i>	14
ABSTRACTS	16
DIVERTICULA OF THE DUODENUM AND DIABETES— <i>William B. Thorning, Jr., M.D., and Howard F. Root, M.D.</i>	17
SECTION II—EXPERIMENTAL PHYSIOLOGY	
STUDIES ON THE NEUTRALIZATION OF GASTRIC ACIDITY— <i>Robert Elman, M.D., and J. Wendell MacLeod, M.D.</i>	21
ABSTRACTS	26
SECTION III—NUTRITION	
GLYCOSURIA AND LACTOSURIA OF PREGNANT AND OF LACTATING WOMEN— <i>Henry J. Brock, M.D., and Roger S. Hubbard, Ph.D.</i>	27
DRY NATURAL DIGESTIVE JUICES— <i>W. N. Boldyreff, M.D.</i>	33
ABSTRACTS	37
SECTION IV—ROENTGENOLOGY	
EMPTIED STOMACH: A REVIEW— <i>Roy Upham, M.D., F.A.C.S.</i>	38
ABSTRACTS	42
SECTION V—THERAPEUTICS	
THERAPY OF NON-MALIGNANT BILIARY TRACT LESIONS— <i>Allen O. Whipple, M.D.</i>	44
ABSTRACTS	46
SECTION VI—ABDOMINAL SURGERY	
DIAGNOSIS AND TREATMENT OF AMEBIC ABSCESS OF THE LIVER— <i>Alton Ochsner, M.D., and Michael DeBakey, M.D.</i>	47
ABSTRACTS	51
SECTION VII—SURGERY OF THE LOWER COLON AND RECTUM	
PRURITIS ANI—A NEW TREATMENT— <i>Nathan J. Simmons, M.D.</i>	53
SECTION VIII—EDITORIAL	
GENERAL PRINCIPLES INVOLVED IN THE DIAGNOSIS OF GASTRO-INTESTINAL DISEASE— <i>Harlow Brooks, M.D.</i>	56
ENTEROGASTRONE— <i>A. C. Ivy, M.D.</i>	58
SECTION IX—BOOK REVIEWS	
TREATMENT BY DIET— <i>Clifford J. Barborka, M.D., Sc.D., F.A.C.P.</i>	59
CIRUGIA GASTRICA—VOL. I— <i>Dr. M. Corachan</i>	61
FOOD FOR THE DIABETIC— <i>Mary P. Huddleson, Consulting Dietitian</i>	61

PUBLISHED MONTHLY BY THE SANDFIELD PUBLISHING CO., FORT WAYNE, INDIANA

of BOW

■ Corrective treatment in spastic and atonic constipation aims to cooperate with Nature toward promoting reflex colonic peristalsis.

This cannot be accomplished satisfactorily by cathartic drugs, purging salines, distending bulk, trick foods, and "roughage", which irritate and over-stimulate the intestine. Mineral oil preparations likewise offer the disadvantage of leakage, and by hastening the current, interfere with digestion.

IDEAL TREATMENT

The persistent search for an agent which would encourage physiologic functional activity naturally and effectively in the treatment of the sluggish or irritated colon, results in Metamucil—an outgrowth of the mucin idea—clinically practical, easy to take, inexpensive and functionally a success.

METAMUCIL

SEARLE

WHAT IS METAMUCIL? Metamucil is a purified, concentrated vegetable mucilloid prepared from the seed of *Plantago Ovata* (Forsk), freed of all solid particles, and held in dispersion with a specially prepared milk powder.

WHAT DOES METAMUCIL DO? Metamucil helps to promote and regulate intestinal peristalsis by providing the lubricant effect of the normal human secretion, supplying the bland, easily compressed bulk necessary for fecal propulsion.

A VALUABLE ADJUVANT IN PEPTIC ULCER

Although chemically unrelated to mucin, Metamucil is similar in physical characteristics. It has been found a valuable aid in the treatment of gastric and duodenal ulcer in this way: Metamucil forms a mucilaginous gel which renders the stomach contents less irritating to the ulcer crater; it is mildly acid adsorbent—reduces amount of alkali needed; it helps correct accompanying colonic dysfunction and pain.

G.D. Searle & Co.

FINE PHARMACEUTICALS SINCE 1888

CHICAGO

LOS ANGELES

KANSAS CITY

SPOKANE

G. D. SEARLE & CO., 4737 Ravenswood Ave., Chicago, Illinois

Gentlemen: You may send me FREE OF CHARGE sample and literature on METAMUCIL.

ATONIC COLON—

Metamucil aids by producing a soft, formed, plastic, mucilaginous, lubricating, non-irritating fecal mass

SPASTIC COLON—

Metamucil produces a bland and lubricating effect which enables the food residue more readily to pass through the narrowed lumen

S. M. S. MEDICAL COLLEGE,
LIBRARY,

R. No. 9215

Date 22-6-71

ULCERATED COLON—

By mixing with and partially enveloping rough and undigested food particles, a soothing and protective effect is produced by the use of Metamucil (Searle)

Metamucil (Searle) is supplied in 1-lb. and 6-oz. containers.

MAKE A TEST

Metamucil is as easy to take as it is effective. We invite you to make a test—Free. The coupon is for your convenience in requesting sample and literature.

Dept. D. N. 3

AMERICAN JOURNAL OF DIGESTIVE DISEASES AND NUTRITION

The Official Publication of

THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

CONTENTS

SECTION I—CLINICAL MEDICINE

	Page
VACCINE THERAPY IN ULCERATIVE COLITIS— <i>Sibrand Lups, M.D.</i> - - - - -	65
UNRECOGNIZED "STROKES" AND THE GASTRO-ENTEROLOGIST— <i>Walter C. Alvarez, M.D.</i> - - - - -	90
LIVER FUNCTION IN HEPATIC AND EXTRAHEPATIC DISEASES— <i>G. K. Wever, M.D.; T. L. Althausen, M.D.; G. R. Biskind, M.D., and Wm. J. Kerr, M.D.</i> - - - - -	93
ABSTRACTS - - - - -	100

SECTION II—EXPERIMENTAL PHYSIOLOGY

DECOMPRESSION OF THE OBSTRUCTED BILIARY SYSTEM OF THE CAT— <i>Harold L. Stewart, M.D., and Abraham Cantarow, M.D.</i> - - - - -	101
THE PARALLEL CONCENTRATION OF ENZYMES IN THE PANCREATIC JUICE— <i>Stewart G. Baxter, M.D., Ph.D.</i> - - - - -	108
ABSTRACTS - - - - -	111

SECTION III—NUTRITION

MILK— <i>Horace W. Soper, M.D.</i> - - - - -	113
ABSTRACTS - - - - -	116

SECTION IV—ROENTGENOLOGY

DYSPHAGIA—ROENTGENOLOGICALLY CONSIDERED— <i>L. S. Otell, M.D., and Fred O. Coe, M.D.</i> - - - - -	117
ABSTRACTS - - - - -	126

SECTION VIII—EDITORIAL

THE CONCEPT OF "COMBINED ACIDITY" IN GASTRIC JUICE STUDIES— <i>Franklin Hollander, Ph.D.</i> - - - - -	127
IS THE PUBLIC BEING STAMPEDED IN REGARD TO VITAMINS?— <i>Walter C. Alvarez, M.D.</i> - - - - -	128
D. SIBRAND LUPS' MONOGRAPH CONCERNING "CHRONIC ULCERATIVE COLITIS" AND AN APPRECIATION OF ITS TRANSLATION INTO ENGLISH BY DR. ABEL J. BAKER— <i>Frank Smithies, M.D.</i> - - - - -	130

SECTION IX—BOOK REVIEWS

THE PHYSIOLOGY OF THE GALLBLADDER— <i>A. C. Ivy, M.D.</i> - - - - -	131
THE AUTOMATIC DISEASES OR THE RHEUMATIC SYNDROME— <i>T. M. Rivers, M.D.</i> - - - - -	133

SECTION XI—SOCIETIES, PROGRAMS AND PROCEEDINGS

PROGRAM OF THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION - - - - -	133
--	-----

SECTION XII—THE CLINIC

TRAUMATIC DUODENAL ULCER IN A 10 YEAR OLD BOY— <i>Jack Witherspoon, M.D.</i> - - - - -	135
--	-----

PUBLISHED MONTHLY BY THE SANDFIELD PUBLISHING CO.

Clinicians, bacteriologists and pathologists unanimously agree that, so far as possible, the alimentary-tract content of pathogenic bacteria and their harmful products should be reduced.

Alpha-Naphco, whether as such or in the jelly-form, by rigid and unbiased laboratory tests (on both man and animals) has been found to be a very potent preparation in reducing the number or inhibiting the growth of pathogenic organisms present in the lower bowel. No evidences of toxicity have been observed even when the preparations have been given in dosage far greater than called for clinically.

The preparation is dispensed as Liquid Alpha-Naphco Germicide and the Jelly of Alpha-Naphco in Enteric-Coated Capsules. Beneficial results, in-so-far as reduction of the number and kind of pathogenic bacteria are concerned, have been achieved by the daily administration of these products in suitable dosage.

No evidence has been brought forth that normal digestive functions are disturbed while Liquid Alpha-Naphco Germicide and the Jelly of Alpha-Naphco in Enteric-Coated Capsules are being exhibited.

The Manufacturer, a trained laboratory investigator, would appreciate Clinicians in Institutions as well as general practitioners, putting Liquid Alpha-Naphco Germicide and the Jelly of Alpha-Naphco in Enteric-Coated Capsules to actual test.

It would seem that these preparations are capable of acting favorably in chronic ulcerative colitis, amebiasis accompanied by the presence of dysentery-producing organisms, acute "Summer" dysentery of children, ordinary bacillary dysentery and kindred affections.

If applied for upon physicians' stationery or their prescription blanks, the Manufacturer is willing to forward a liberal supply of Liquid Alpha-Naphco Germicide and the Jelly of Alpha-Naphco in Enteric-Coated Capsules for actual trial. With the trial samples, data respecting research and clinical investigations also will be sent.

Enquirers Should Address

CAREL LABORATORIES

REDONDO BEACH, CALIFORNIA

NOTE:—These preparations are not and never will be offered through channels other than those concerned with the medical profession.

AMERICAN JOURNAL OF DIGESTIVE DISEASES AND NUTRITION

The Official Publication of
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

CONTENTS

	Page
SECTION I—CLINICAL MEDICINE	
VACCINE THERAPY IN ULCERATIVE COLITIS— <i>Sibrand Lups, M.D.</i> - - - - -	139
HEPATOPTOSIS— <i>Charles W. McClure, M.D.; Herman A. Osgood, M.D., and J. P. Bill, M.D.</i> - - - - -	161
LIVER FUNCTION IN HEPATIC AND EXTRAHEPATIC DISEASES— <i>G. R. Biskind, M.D.; T. L. Althausen, M.D.; G. K. Wever, M.D., and Wm. J. Kerr, M.D.</i> - - - - -	167
ABSTRACTS - - - - -	173
SECTION II—EXPERIMENTAL PHYSIOLOGY	
DECOMPRESSION OF THE OBSTRUCTED BILIARY SYSTEM IN THE CAT— <i>Abraham Cantarow, M.D.; Harold L. Stewart, M.D., and Stanley G. McCool, M.D.</i> - - - - -	174
ABSTRACTS - - - - -	177
SECTION III—NUTRITION	
CLINICAL EVIDENCE OF FIFTY SO-CALLED GASTROINTESTINAL DISEASES WHICH REALLY ARE CAUSED BY FOOD ALLERGY WITH DISCUSSION OF THEIR TREATMENT— <i>Josef S. Smul, M.D.</i> - - - - -	178
SECTION IV—ROENTGENOLOGY	
DIVERTICULAR SARCOMA OF THE STOMACH— <i>James T. Case, M.D., F.A.C.S.</i> - - - - -	185
ABSTRACTS - - - - -	188
SECTION V—THERAPEUTICS	
THE USE OF DUODENAL EXTRACT AS AN ADJUVANT IN THE TREATMENT OF BENIGN PEPTIC LESIONS: REPORT OF EIGHT CASES— <i>Andrew B. Rivers, M.D.</i> - - - - -	189
ABSTRACTS - - - - -	195
SECTION VII—SURGERY OF THE LOWER COLON AND RECTUM	
THE MODERN PROCTOLOGIC CLINIC— <i>Martin J. Synnott, M.A., M.D., F.A.C.P.</i> - - - - -	196
SECTION VIII—EDITORIAL	
THE COMMON PATHOGENESIS OF TERMINAL ILEITIS, IDIOPATHIC ULCERATIVE COLITIS AND BACILLARY DYSENTERY— <i>Walter A. Bastedo, M.D.</i> - - - - -	201
NEW YORK CITY ACTIVE FOR THE AMERICAN BOARD OF GASTROENTEROLOGY— <i>Anthony Bassler, M.D.</i> - - - - -	201
SECTION IX—BOOK REVIEWS	
DIET MANUAL, ST. MARY'S HOSPITAL— <i>Sister Mary Victor, R.N., B.S.</i> - - - - -	202
SECTION XI—SOCIETIES, PROGRAMS AND PROCEEDINGS	
FINAL PROGRAM OF THE THIRTY-EIGHTH ANNUAL MEETING OF THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION - - -	203
SECTION XII—"THE CLINIC"	
AN UNUSUAL CASE OF PRIMARY ACTINOMYCOSIS INVOLVING THE MESENTERY OF THE SMALL INTESTINE— <i>C. J. Tidmarsh, M.A., M.D., F.R.C.P.(C)</i> - - - - -	205
INCOMPLETE INTESTINAL OBSTRUCTION DUE TO SHORTENED LIGAMENT OF TREITZ— <i>Joseph Stein, M.D.</i> - - - - -	208

PUBLISHED MONTHLY BY THE SANDFIELD PUBLISHING CO.

ELI LILLY AND COMPANY

FOUNDED 1876

Makers of Medicinal Products

S U R G E R Y *In Diabetes*

~~~~~

Before Insulin the inability to protect the diabetic from serious medical complications made surgical operations inadvisable except in the more urgent cases. Today the diabetic patient, under proper dietetic control and treatment with Insulin, stands surgery almost as well as the nondiabetic.

*letin (Insulin, Lilly) is supplied through the drug trade in 5 cc. and 10 cc. vials.*

*Prompt Attention Given to Professional Inquiries*

PRINCIPAL OFFICES AND LABORATORIES, INDIANAPOLIS, INDIANA, U. S. A.

# AMERICAN JOURNAL OF DIGESTIVE DISEASES AND NUTRITION

The Official Publication of  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

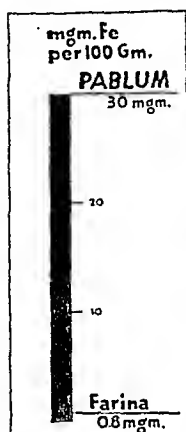
## CONTENTS

|                                                                                                                                                                    | Page |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| SECTION I—CLINICAL MEDICINE                                                                                                                                        |      |
| INTESTINAL TUBERCULOSIS: A CLINICAL, ROENTGENOLOGICAL AND PATHOLOGICAL STUDY OF 2086 PATIENTS AFFECTED WITH PULMONARY TUBERCULOSIS— <i>Emil Granet, A.B., M.D.</i> | 209  |
| STOMACH LAVAGE MICROSCOPY AS AN AID IN THE DIAGNOSIS OF BILIARY TRACT DISEASE— <i>Henry A. Rafsky, M.D., F.A.C.P.</i>                                              | 214  |
| A CLINICAL INTERPRETATION OF DUODENAL DIVERTICULUM— <i>Herman H. Riecker, M.D.</i>                                                                                 | 217  |
| SECTION II—EXPERIMENTAL PHYSIOLOGY                                                                                                                                 |      |
| THE MECHANISM OF THE DELAY IN GASTRIC EMPTYING TIME CAUSED BY ANOXEMIA— <i>George Crisler, Ph.D., M.D.; E. J. Van Liere, Ph., M.D., and I. A. Wiles, M.S.</i>      | 221  |
| QUANTITATIVE ESTIMATION OF ENZYME CONCENTRATION IN DUODENAL FLUIDS: A PRACTICAL CLINICAL METHOD— <i>Charles W. Lueders, M.D.</i>                                   | 224  |
| THE ORIGIN AND SIGNIFICANCE OF THE BLOOD SERUM ENZYMES— <i>Lathan A. Crandall, Jr., M.D., Ph.D.</i>                                                                | 230  |
| ABSTRACTS                                                                                                                                                          | 235  |
| SECTION III—NUTRITION                                                                                                                                              |      |
| INSULIN-GLUCOSE THERAPY IN HEART DISEASE— <i>E. Sterling Nichol, M.D.</i>                                                                                          | 236  |
| ACID-BASE AND ASSIMILABILITY OF FRUIT JUICES— <i>I. Newton Kugelmann, M.D.</i>                                                                                     | 242  |
| A NEW CONCEPT OF MENIERE'S DISEASE AND ITS RESPONSE TO ANTIRETENTIONAL THERAPY— <i>Eugene Foldes, M.D.</i>                                                         | 243  |
| ABSTRACTS                                                                                                                                                          | 247  |
| SECTION IV—ROENTGENOLOGY                                                                                                                                           |      |
| CARCINOMA OF THE BODY OF THE PANCREAS: A CLINICO-ROENTGENOLOGIC DIAGNOSIS— <i>Martin G. Vorhaus, M.D.</i>                                                          | 248  |
| DIVERTICULUM OF THE STOMACH— <i>Ellis B. Freilich, M.D.; Gerhard Danielius, M.D., and George C. Coc, M.D.</i>                                                      | 252  |
| ABSTRACTS                                                                                                                                                          | 254  |
| SECTION V—THERAPEUTICS                                                                                                                                             |      |
| TREATMENT OF HEMORRHAGE CAUSED BY PEPTIC ULCER— <i>G. A. Hendon, M.D.</i>                                                                                          | 255  |
| ABSTRACTS                                                                                                                                                          | 257  |
| SECTION VI—ABDOMINAL SURGERY                                                                                                                                       |      |
| FACTORS PERTINENT TO THE REDUCTION OF THE MORTALITY IN CHOLECYSTECTOMY— <i>Moses Behrend, M.D., F.A.C.S.</i>                                                       | 258  |
| ABSTRACTS                                                                                                                                                          | 260  |
| SECTION VIII—EDITORIAL                                                                                                                                             |      |
| ADVERTISEMENTS SHOULD BE READ— <i>Frank Smithies, M.D.</i>                                                                                                         | 261  |
| ABANDONING FREE REPRINTS— <i>Frank Smithies, M.D.</i>                                                                                                              | 262  |
| SECTION IX—BOOK REVIEWS                                                                                                                                            |      |
| PHYSIOLOGY IN MODERN MEDICINE— <i>J. J. R. Macleod, M.B., LL.D., D.Sc., F.R.C.P., F.R.S.</i>                                                                       | 262  |
| EMOTIONS AND BODILY CHANGES— <i>H. Flanders Dunbar, M.D., Ph.D.</i>                                                                                                | 263  |
| SECTION X—AFTER "HOURS"                                                                                                                                            |      |
| AN EXHIBITION OF BOOKS ILLUSTRATING THE PROGRESS OF GASTROENTEROLOGY SHOWN AT THE GRADUATE FORTNIGHT— <i>Burrill B. Crohn, M.D., and B. D. Rosenak, M.D.</i>       | 264  |
| ABSTRACTS                                                                                                                                                          | 271  |
| SECTION XII—THE CLINIC                                                                                                                                             |      |
| GASTRIC ULCER FOLLOWING DUODENAL ULCER WITH OBSTRUCTION: REPORT OF A CASE— <i>Fred R. Harper, M.D.</i>                                                             | 271  |

PUBLISHED MONTHLY BY THE SANDFIELD PUBLISHING CO.

# For bland diet therapy, especially ULCER cases—PABLUM

**F**AR too often the bland diet prescribed for gastric ulcer, colitis, and similar gastro-intestinal disorders is a deficient diet. An analysis made by Troutt of ulcer diets used by 6 leading hospitals in different sections of the country showed them to be "well below the Sherman standard of 15 milligrams" in iron and low in the water-soluble vitamins.<sup>1</sup> "Vitamin B would appear to be represented at a maintenance level in most cases," writes Troutt, "but the possible relation of vitamin B to gastro-intestinal function and appetite should make one pause before accepting a low standard."



Although Pablum has a low fiber content it is 37 times richer than farina in iron and in calcium, 4 times richer in phosphorus, and  $4\frac{1}{2}$  times richer in copper.

## Low in Fiber—High in Iron

Pablum is the only food rich in a wide variety of the accessory food factors that can be fed over long periods of time without danger of gastro-intestinal irritation. Its fiber content is only 0.9%. Yet Pablum contains 37 times more iron than farina and is an excellent source (+ + +) of vitamins B and G, in which farina is deficient. Supplying  $8\frac{1}{2}$  mgms. iron per ounce, Pablum is 8 times richer than spinach in iron.

## Rich in Vitamin B

The high vitamin B content of Pablum assumes new importance in light of recent laboratory studies showing that avitaminosis B predisposes to certain gastro-intestinal disorders. Apropos of this, Cowgill says, "Gastric ulcer is another disorder which can conceivably be related to vitamin B deficiency. Insofar as the treatment of this condition usually involves a marked restriction of diet the occurrence of at least a moderate shortage of this vitamin is by no means unlikely."

Requiring no further cooking, Pablum is especially valuable during the healing stage of ulcer when the patient is back at work but still requires frequent meals. Pablum can be prepared quickly and conveniently at the office or shop simply by adding milk or cream and salt and sugar to taste. Pablum has the added advantage that it can be prepared in many varied ways—in muffins, mush, puddings, junket, etc. Further, Pablum is so thoroughly cooked that its cereal-starch has been shown to be more quickly digested than that of farina, oatmeal, cornmeal, or whole wheat cooked four hours in a double boiler (studies *in vitro* by Ross and Burrill). In addition to the above advantages, Pablum is the only base-forming cereal (except Mead's Cereal which is the uncooked form of Pablum).

Pablum (Mead's Cereal thoroughly pre-cooked) consists of wheatmeal, oatmeal, cornmeal, wheat embryo, alfalfa, yeast, beef bone, iron salt and sodium chloride. <sup>1,2</sup> Bibliography on request.

**MEAD JOHNSON & COMPANY - - Evansville, Indiana, U.S.A.**

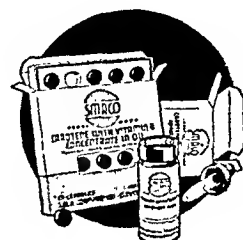
Please enclose professional card when requesting samples of Mead Johnson products to cooperate in preventing their reaching unauthorized persons.



## NATURE OFFERS CAROTENE [PRO-VITAMIN A] IN FRUITS AND VEGETABLES



S. M. A. Corporation offers CAROTENE (PRO-VITAMIN A) concentrated in a vegetable oil vehicle in capsule and liquid forms, alone and in combination with Vitamin D Concentrate. Council accepted.



**S.M.A. CORPORATION • CLEVELAND, OHIO**

# AMERICAN JOURNAL OF DIGESTIVE DISEASES AND NUTRITION

The Official Publication of  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTENTS

|                                                                                                                                                                            | Page |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| SECTION I—CLINICAL MEDICINE                                                                                                                                                |      |
| RECENT DEVELOPMENT IN THE STUDY OF ORAL BACTERIAL FLORA— <i>Lloyd Arnold, M.D., and Carroll W. Stuart, D.D.S., M.D.</i>                                                    | 275  |
| GASTROSCOPY: PAST, PRESENT AND FUTURE— <i>Edwin Boros, M.D.</i>                                                                                                            | 280  |
| A NEW TUBE FOR ANAESTHETIZATION OF THE HYPOPHARYNX— <i>Rudolf Schindler, M.D.</i>                                                                                          | 281  |
| ABSTRACTS                                                                                                                                                                  | 282  |
| SECTION II—EXPERIMENTAL PHYSIOLOGY                                                                                                                                         |      |
| A SYMPOSIUM CONCERNED WITH THE DUODENAL FACTORS IN THE NEUTRALIZATION OF ACID CHYME— <i>Frank C. Mann, M.D., and Jesse L. Bollman, M.D.</i>                                | 284  |
| THE REACTION OF THE CONTENT OF THE ISOLATED DUODENUM— <i>Pat R. Imes, M.D.</i>                                                                                             | 285  |
| THE CAPACITY OF THE DUODENUM TO NEUTRALIZE, BUFFER AND TO DILUTE ACID— <i>G. Arnold Stevens, M.D.</i>                                                                      | 288  |
| THE REACTION OF THE DUODENAL CONTENT AFTER EXCLUSION OF BILE FROM THE DUODENUM— <i>Jerry W. McRoberts, M.D.</i>                                                            | 293  |
| THE EFFECT OF EXCLUSION OF THE PANCREATIC SECRETION BY EVULSION OF THE PANCREATIC DUCTS ON THE REACTION OF THE DUODENAL CONTENT— <i>M. Tischer Hoerner, M.D.</i>           | 295  |
| THE EFFECT OF EXCLUSION OF THE PANCREATIC SECRETION BY A PANCREATIC FISTULA ON THE REACTION OF THE GASTRIC, DUODENAL AND JEJUNAL CONTENTS— <i>M. Tischer Hoerner, M.D.</i> | 298  |
| THE BUFFER CAPACITY OF THE PANCREATIC JUICE— <i>M. Tischer Hoerner, M.D.</i>                                                                                               | 300  |
| PEPTIC ULCER FOLLOWING LOSS OF PANCREATIC SECRETION THROUGH A FISTULA: AN EXPERIMENTAL STUDY— <i>M. Tischer Hoerner, M.D.</i>                                              | 302  |
| ABSTRACTS                                                                                                                                                                  | 305  |
| SECTION III—NUTRITION                                                                                                                                                      |      |
| PROTECTION OF NUTRITION DURING THE USE OF "ELIMINATION DIETS"— <i>Albert H. Rowe, M.D.</i>                                                                                 | 306  |
| ABSTRACTS                                                                                                                                                                  | 307  |
| SECTION IV—ROENTGENOLOGY                                                                                                                                                   |      |
| DIAPHRAGMATIC HERNIA: WITH A REPORT OF TEN CASES OF OESOPHAGEAL ORIFICE HERNIA— <i>Katherine S. Andrews, M.D.</i>                                                          | 310  |
| SECTION VI—ABDOMINAL SURGERY                                                                                                                                               |      |
| THE USE OF METAL CLIPS IN GASTROINTESTINAL ANASTOMOSIS— <i>Ralph B. Bettman, M.D., and Leo M. Zimmerman, M.D.</i>                                                          | 318  |
| ABSTRACTS                                                                                                                                                                  | 321  |
| SECTION VIII—EDITORIALS                                                                                                                                                    |      |
| PASSAGE OF NATIVE PROTEINS THROUGH THE NORMAL GASTRO-INTESTINAL WALL— <i>Bret Ratner, M.D.</i>                                                                             | 324  |
| BREVITY— <i>Frank Smithies, M.D.</i>                                                                                                                                       | 325  |
| SECTION IX—BOOK REVIEWS                                                                                                                                                    |      |
| BODY MECHANICS IN THE STUDY AND TREATMENT OF DISEASE— <i>J. E. Goldthwait, L. T. Brown, L. T. Swain, and J. G. Kuhns</i>                                                   | 326  |
| METHODS OF TREATMENT— <i>Logan Clendening, M.D.</i>                                                                                                                        | 326  |
| ABSTRACTS                                                                                                                                                                  | 327  |
| SECTION XII—"THE CLINIC"                                                                                                                                                   |      |
| AN INSTANCE OF MARKED ABDOMINAL DISTENTION WITH THE PROBABLE ETIOLOGIC FACTORS BEING ABNORMAL ENDOCRINE FUNCTION— <i>George B. Dorff, M.D.</i>                             | 328  |

PUBLISHED MONTHLY BY THE SANDFIELD PUBLISHING CO.



“ . . . we know that in the infant and growing child alkali in excess of acid must be stored.”

**BUT—**

*Growth and Development of the Child, Part III, White House Conference on Child Health and Protection, New York, 1932, p. 213.*

## many diets are acid-forming

AS pointed out in the Journal of the American Medical Association (Queries and Minor Notes, 103:701, 1934), “. . . most high carbohydrate foods of the artificial and refined types are lacking in the basic elements. These basic ions, such as sodium, potassium, and calcium, are necessary for the neutralization and excretion of the various acid waste products of the body. Hence carbohydrates may be implicated in the occurrence of such an acid state by displacing other necessary food products from the dietary.”

Ordinary cereals and cereal products, meat, and eggs—all produce an acid ash when burned in the body, yet they form the mainstay of the average diet. Although this preponderance of acid-forming foods is not definitely known to have great significance for the health of normal adults, a number of authorities advocate a basic or alkali-forming diet for children and pregnant women.

**INFANCY AND CHILDHOOD.** “Alkaline diets are essential for infancy where growth is rapid,” declares Shohl. He calculates the need as 10 cc. excess of 0.1 normal base per kilo per day.<sup>1</sup> Babies fed on breast milk stored an excess of base over acid, the range being from 31 to 56 cc. 0.1 N base per day, is the finding of the Committee on Growth and Development of the White House Conference on Child Health.<sup>2</sup> Lippard and Marples observed greater increases in weight of infants receiving basic diets as compared with controls on acid-forming feedings.<sup>3</sup>

**PREGNANCY AND LACTATION.** Shohl states, “Pregnancy and lactation require additional alkali—a minimum of 150 cc. 0.1 N base per day.”<sup>4</sup> Coons and associates, from acid-base balances taken upon normal pregnant women receiving basic diets, determined that the storage of basic substances was even greater than estimated by Shohl. “This may be some indication,” they say, “of the magnitude of the maternal needs exclusive of fetus.”<sup>5</sup>

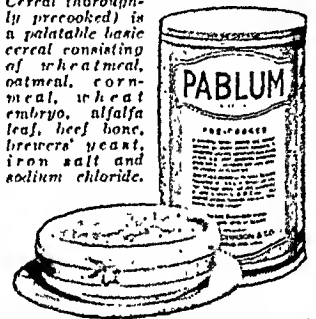
As the chief alkali-forming foods are fruits, vegetables, and milk, the ordinary basic diet consisting of these foods is likely to be low in calories and often does not appease hunger. But Pablum—the only base-forming cereal\*—offers a way to add muffins, cereal, puddings and similar “filling” foods to the usual basic diet. Pablum, moreover, is richer than ordinary cereals in calcium, phosphorus, iron, and copper and supplies vitamins A, B, E, and G.

<sup>1-4</sup> Bibliography on request.

\*Mead's Cereal (Pablum in uncooked form) is also base-forming.

**MEAD JOHNSON & COMPANY, - - - Evansville, Indiana, U.S.A.**

Pablum (Mead's Cereal thoroughly precooked) is a palatable basic cereal consisting of wheatmeal, oatmeal, cornmeal, wheat embryo, alfalfa leaf, beef bone, brewers' yeast, iron salt and sodium chloride.



| Cereal       | Base | Acid |
|--------------|------|------|
| PABLUM       | 1.8  |      |
| Farina       |      | 11.0 |
| Oatmeal      |      | 12.9 |
| Wheat, whole |      | 11.5 |
| Cornmeal     |      | 5.3  |
| Barley       |      | 10.1 |
| Rice         |      | 8.1  |

Figures given in the above table are based on 100 grams of food and represent cubic centimeters of normal acid or base.

# AMERICAN JOURNAL OF DIGESTIVE DISEASES AND NUTRITION

The Official Publication of  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTENTS

### SECTION I—CLINICAL MEDICINE

|                                                                                                                                                                                                                          |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| ON THE ETIOLOGY OF PEPTIC ULCER—AN ANALYSIS OF 70 ULCER PATIENTS— <i>Samuel C. Robinson, M.D.</i> - - - - -                                                                                                              | 333 |
| A FOLLOW-UP OF ULCERATIVE COLITIS (NON-SPECIFIC)— <i>Burrill B. Crohn, M.D., and Bernard D. Rosenak, M.D.</i> - - - - -                                                                                                  | 343 |
| THE ACUTELY ILL, JAUNDICED PATIENT: A REPORT OF TWENTY-ONE INSTANCES OF HEPATIC ICTERUS, SEVEN OF WHOM HAD HIGH BLOOD NITROGEN— <i>S. G. Meyers, M. D.; Osborne A. Brines, M.D., and Benjamin Juliar, M.D.</i> - - - - - | 346 |
| A CLINICAL REVIEW OF GIARDIASIS—TWENTY-TWO CASES OBSERVED DURING STUDY OF 572 PRIVATE PATIENTS— <i>G. S. dePaula e Silva, M.D.</i> - - - - -                                                                             | 350 |
| A CONSIDERATION OF THE PATIENT WITH GASTROINTESTINAL COMPLAINTS BUT WHO IS WITHOUT EVIDENCES OF ORGANIC PATHOLOGY— <i>G. Alexander Young, M.D., and Richard H. Young, M.D.</i> - - - - -                                 | 353 |
| NON-TUBERCULOUS MESENTERIC LYMPHADENITIS IN CHILDHOOD— <i>Louis H. Sagar, M.D., and B. D. Rosenak, M. D.</i> - - - - -                                                                                                   | 356 |
| ABSTRACTS - - - - -                                                                                                                                                                                                      | 360 |

### SECTION II—EXPERIMENTAL PHYSIOLOGY

|                                                                                                                                                                                   |     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| THE EFFECT OF OXYGEN INHALATION ON GASEOUS DISTENTION OF THE STOMACH AND THE SMALL INTESTINE— <i>Jacob Fine, M.D.; John B. Sears, M.D., and Benjamin M. Banks, M.D.</i> - - - - - | 361 |
| ABSTRACTS - - - - -                                                                                                                                                               | 367 |

### SECTION III—NUTRITION

|                                                                                                                                                             |     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| THE ROLE OF SERUM-CALCIUM FRACTIONS IN THE EFFECT OF VIOSTEROL ON THE BLEEDING TENDENCY IN JAUNDICE— <i>J. S. Gray, M.S., and A. C. Ivy, M.D.</i> - - - - - | 368 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|

### SECTION IV—ROENTGENOLOGY

|                                                                                                                                                                                    |     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| APPENDICEAL ABSCESS: A ROENTGENOLOGIC CONSIDERATION, WITH ESPECIAL REFERENCE TO THE DIAGNOSTIC DIFFICULTIES AND ITS DIFFERENTIAL DIAGNOSIS— <i>Maurice Feldman, M.D.</i> - - - - - | 373 |
| ABSTRACTS - - - - -                                                                                                                                                                | 378 |

### SECTION V—THERAPEUTICS

|                                                                                                                                          |     |
|------------------------------------------------------------------------------------------------------------------------------------------|-----|
| A SYMPOSIUM ON MANAGEMENT OF OESOPHAGITIS— <i>Walter A. Bastedo, M.D.; Julius Friedenwald, M.D., and Horace W. Soper, M.D.</i> - - - - - | 379 |
|------------------------------------------------------------------------------------------------------------------------------------------|-----|

### SECTION VIII—EDITORIAL

|                                                                                                                                                |     |
|------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| GREETINGS TO THE SPANISH JOURNAL OF DISEASES OF THE DIGESTIVE APPARATUS AND OF NUTRITION— <i>The Editorial Council</i> - - - - -               | 380 |
| AMERICAN BOARD OF GASTROENTEROLOGY— <i>A. F. R. Andresen, M.D.</i> - - - - -                                                                   | 380 |
| REPORT OF THE PRESIDENT— <i>A. F. R. Andresen, M.D.</i> - - - - -                                                                              | 380 |
| REPORT FROM AMERICAN BOARD OF GASTROENTEROLOGY TO THE SECTION OF GASTROENTEROLOGY AND PROCTOLOGY OF THE AMERICAN MEDICAL ASSOCIATION - - - - - | 381 |
| CHOLESTEROL— <i>Horace W. Soper, M.D.</i> - - - - -                                                                                            | 381 |

### SECTION IX—BOOK REVIEWS

|                                                                                                                                        |     |
|----------------------------------------------------------------------------------------------------------------------------------------|-----|
| RADIOLOGIC CLINIQUE DU TUBE DIGESTIF, PUBLICE SOUS LA DIRECTION SE MM.— <i>Pierre Duval, Jean-Charles Roux, Henri Bécère</i> - - - - - | 382 |
| TEXTBOOK OF BIOCHEMISTRY— <i>Harrow and Sherwin</i> - - - - -                                                                          | 384 |

### SECTION XI—SOCIETIES, PROGRAMS AND PROCEEDINGS

|                                                                                          |     |
|------------------------------------------------------------------------------------------|-----|
| CHANGES IN MEMBERSHIP, COMMITTEES, ETC.— <i>Russell S. Bolcs, M.D., Sec'y.</i> - - - - - | 385 |
|------------------------------------------------------------------------------------------|-----|

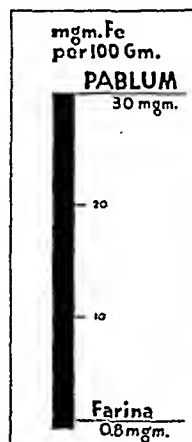
### SECTION XII—"THE CLINIC"

|                                                                                 |     |
|---------------------------------------------------------------------------------|-----|
| A CASE OF GASTRIC POLYPOSIS— <i>A. C. van Ravenswaay, M.D.</i> - - - - -        | 386 |
| NON-TROPICAL SPRUE: REPORT OF A CASE— <i>John A. Reed, A.B., M.D.</i> - - - - - | 388 |
| ABSTRACTS - - - - -                                                             | 390 |

PUBLISHED MONTHLY BY THE SANDFIELD PUBLISHING CO.

# For bland diet therapy, especially ULCER cases—PABLUM

**F**AR too often the bland diet prescribed for gastric ulcer, colitis, and similar gastro-intestinal disorders is a deficient diet. An analysis made by Troutt of ulcer diets used by 6 leading hospitals in different sections of the country showed them to be "well below the Sherman standard of 15 milligrams" in iron and low in the water-soluble vitamins. "Vitamin B would appear to be represented at a maintenance level in most cases," writes Troutt, "but the possible relation of vitamin B to gastro-intestinal function and appetite should make one pause before accepting a low standard."



Although Pablum has a low fiber content it is 37 times richer than farina in iron and in calcium, 4 times richer in phosphorus, and 4½ times richer in copper.

## Low in Fiber—High in Iron

Pablum is the only food rich in a wide variety of the accessory food factors that can be fed over long periods of time without danger of gastro-intestinal irritation. Its fiber content is only 0.9%. Yet Pablum contains 37 times more iron than farina and is an excellent source (+ + +) of vitamins B and G, in which farina is deficient. Supplying 8½ mgms. iron per ounce, Pablum is 8 times richer than spinach in iron.

Requiring no further cooking, Pablum is especially valuable during the healing stage of ulcer when the patient is back at work but still requires frequent meals. Pablum can be prepared quickly and conveniently at the office or shop simply by adding milk or cream and salt and sugar to taste. Pablum has the added advantage that it can be prepared in many varied ways—in muffins, mush, puddings, junket, etc. Further, Pablum is so thoroughly cooked that its cereal-starch has been shown to be more quickly digested than that of farina, oatmeal, cornmeal, or whole wheat cooked four hours in a double boiler (studies *in vitro* by Ross and Burrill). In addition to the above advantages, Pablum is the only base-forming cereal (except Mead's Cereal which is the uncooked form of Pablum).

Pablum (Mead's Cereal thoroughly pre-cooked) consists of wheatmeal, oatmeal, cornmeal, wheat embryo, alfalfa, yeast, beef bone, iron salt and sodium chloride. <sup>1,2</sup> Bibliography on request.

**MEAD JOHNSON & COMPANY - - Evansville, Indiana, U. S. A.**

Please enclose professional card when requesting samples of Mead Johnson products to cooperate in preventing their reaching unauthorized persons.

# Sunshine or Not—They Need Vitamin A



## Smaco CAROTENE-in-oil provides Vitamin A activity alone

Adequate summer sun may make added vitamin D in the diet unnecessary but it does not take the place of Vitamin A. • The human body needs Vitamin A activity twelve months of the year, winter and summer, regardless of whether it is exposed to sunshine or

not. • Vitamin A activity in edible fruits and vegetables occurs only in the form of Pro-Vitamin A, (Carotene). • In prescribing Smaco Carotene-in-oil you are providing Vitamin A activity in the same form in which it occurs in fruits and vegetables.

**PROMPT ATTENTION GIVEN PROFESSIONAL INQUIRIES • S. M. A. CORPORATION, CLEVELAND**

# AMERICAN JOURNAL OF DIGESTIVE DISEASES AND NUTRITION

The Official Publication of  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTENTS

### SECTION I—CLINICAL MEDICINE

|                                                                                                                                                                                                | Page |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| A PHILOSOPHIC, CLINICAL AND RETROSPECTIVE DISCUSSION OF CERTAIN MAJOR PROBLEMS IN THE DIGESTIVE FIELD— <i>Thomas R. Brown, M.D.</i>                                                            | 391  |
| MIGRAINE: A COMMON-SENSE APPROACH— <i>Libby Pulsifer, M.D.</i>                                                                                                                                 | 397  |
| THE VALIDITY OF FRACTIONAL GASTRIC ANALYSIS— <i>Frances A. Hellebrandt, M.D., and Elizabeth Brogdon, M.S.</i>                                                                                  | 402  |
| STUDIES ON THE RELATION OF NON-SPECIFIC ULCERATIVE COLITIS TO BACILLARY DYSENTERY (WITH PARTICULAR REFERENCE TO THE DYSENTERY BACTERIOPHAGE)— <i>A. Winkelstein, M.D., and C. Herschberger</i> | 408  |
| ABSTRACTS                                                                                                                                                                                      | 411  |

### SECTION II—EXPERIMENTAL PHYSIOLOGY

|                                                                                                                                                                  |     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| THE PANCREAS AND GENERAL METABOLISM: A PHYSIOLOGICAL, METABOLIC AND PHILOSOPHICAL CONCEPT OF NUTRITIONAL UNITY AND INTERDEPENDENCE— <i>W. N. Boldyreff, M.D.</i> | 413 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|

### SECTION III—NUTRITION

|                                                                                                      |     |
|------------------------------------------------------------------------------------------------------|-----|
| WHAT SHOULD BE THE PER CAPITA PER DAY MILK CONSUMPTION OF OUR POPULATION?— <i>Lloyd Arnold, M.D.</i> | 416 |
| ABSTRACTS                                                                                            | 421 |

### SECTION V—THERAPEUTICS

|                                                                                                                                                                                |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| THE TREATMENT OF FOOD ALLERGY AND INDIGESTION OF PANCREATIC ORIGIN WITH PANCREATIC ENZYMES— <i>Anton W. Oelgoetz, M.D.; Paul A. Oelgoetz, B.A., and Juanita Wittkind, R.N.</i> | 422 |
| HISTIDINE IN THE TREATMENT OF PEPTIC ULCER: A PRELIMINARY REPORT— <i>John T. Eads, M.D.</i>                                                                                    | 426 |
| ABSTRACTS                                                                                                                                                                      | 430 |

### SECTION VI—ABDOMINAL SURGERY

|                                                                                       |     |
|---------------------------------------------------------------------------------------|-----|
| BLEEDING GASTRIC AND DUODENAL ULCERS— <i>A. Philip MacGuire, A.B., M.D., F.A.C.S.</i> | 431 |
| ABSTRACTS                                                                             | 434 |

### SECTION VIII—EDITORIAL

|                                                                                                                                    |     |
|------------------------------------------------------------------------------------------------------------------------------------|-----|
| ON AN ADEQUATE CONCEPTION OF THE ETIOLOGY AND THE SIGNIFICANCE OF PEPTIC ULCER (GASTRIC AND DUODENAL)— <i>Frank Smithies, M.D.</i> | 437 |
|------------------------------------------------------------------------------------------------------------------------------------|-----|

### SECTION IX—BOOK REVIEWS

|                                                                                                                                |     |
|--------------------------------------------------------------------------------------------------------------------------------|-----|
| THE PATIENT AND THE WEATHER, VOL. 2, ANATOMIC DYSINTEGRATION— <i>William F. Peterson, M.D., and Margaret E. Milliken, S.M.</i> | 440 |
| PREVIEW OF DR. B. B. VINCENT LYON'S "ATLAS"                                                                                    | 441 |

### SECTION XII—"THE CLINIC"

|                                                                                          |     |
|------------------------------------------------------------------------------------------|-----|
| TYPICAL AND ATYPICAL TERMINAL ILEITIS— <i>A. Galambos, M.D., and W. Mittelmann, M.D.</i> | 442 |
| INSULIN-GLUCOSE THERAPY IN CORONARY THROMBOSIS— <i>Gerald J. Kohne, M.D.</i>             | 447 |

PUBLISHED MONTHLY BY THE SANDFIELD PUBLISHING CO.

"... we know that in the infant and growing child alkali in excess of acid must be stored."

**BUT—**

## many diets are acid-forming

*Growth and Development of the Child, Part III, White House Conference on Child Health and Protection, New York, 1932, p. 213.*

AS pointed out in the Journal of the American Medical Association (Queries and Minor Notes, 103:701, 1934), "... most high carbohydrate foods of the artificial and refined types are lacking in the basic elements. These basic ions, such as sodium, potassium, and calcium, are necessary for the neutralization and excretion of the various acid waste products of the body. Hence carbohydrates may be implicated in the occurrence of such an acid state by displacing other necessary food products from the dietary."

Ordinary cereals and cereal products, meat, and eggs—all produce an acid ash when burned in the body, yet they form the mainstay of the average diet. Although this preponderance of acid-forming foods is not definitely known to have great significance for the health of normal adults, a number of authorities advocate a basic or alkali-forming diet for children and pregnant women.

**INFANCY AND CHILDHOOD.** "Alkaline diets are essential for infancy where growth is rapid," declares Shohl. He calculates the need as 10 cc. excess of 0.1 normal base per kilo per day.<sup>1</sup> Babies fed on breast milk stored an excess of base over acid, the range being from 31 to 56 cc. 0.1 N base per day, is the finding of the Committee on Growth and Development of the White House Conference on Child Health.<sup>2</sup> Lippard and Marples observed greater increases in weight of infants receiving basic diets as compared with controls on acid-forming feedings.<sup>3</sup>

**PREGNANCY AND LACTATION.** Shohl states, "Pregnancy and lactation require additional alkali—n minimum of 150 cc. 0.1 N base per day."<sup>4</sup> Coons and associates, from acid-base balances taken upon normal pregnant women receiving basic diets, determined that the storage of basic substances was even greater than estimated by Shohl. "This may be some indication," they say, "of the magnitude of the maternal needs exclusive of fetus."<sup>4</sup>

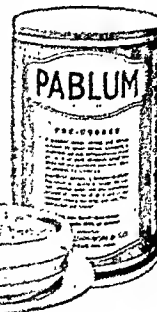
As the chief alkali-forming foods are fruits, vegetables, and milk, the ordinary basic diet consisting of these foods is likely to be low in calories and often does not appease hunger. But Pablum—the only base-forming cereal\*—offers a way to add muffins, cereal, puddings and similar "filling" foods to the usual basic diet. Pablum, moreover, is richer than ordinary cereals in calcium, phosphorus, iron, and copper and supplies vitamins A, B, E, and G.

<sup>1,4</sup> Bibliography on request.

\*Mead's Cereal (Pablum in uncooked form) is also base-forming.

**MEAD JOHNSON & COMPANY, - - - Evansville, Indiana, U.S.A.**

Pablum (Mead's Cereal thoroughly precooked) is a palatable basic cereal consisting of wheatmeal, oatmeal, cornmeal, wheat embryo, alfalfa leaf, beef bone, brewers' yeast, iron salt and sodium chloride.



| Cereal       | Base | Acid |
|--------------|------|------|
| PABLUM       | 1.8  |      |
| Farina       |      | 11.0 |
| Oatmeal      |      | 12.9 |
| Wheat, whole |      | 11.5 |
| Cornmeal     |      | 5.3  |
| Barley       |      | 10.1 |
| Rice         |      | 8.1  |

Figures given in the above table are based on 100 grams of food and represent cubic centimeters of normal acid or base.



Decholin, (dehydrocholic acid), a true choleretic and practically non-toxic, is indicated when stimulation of liver cells to increase the secretion of bile is desired. It has been found distinctly valuable in functional hepatic insufficiency, in cardiac conditions associated with hepatic dysfunction and ascites, and in toxemias due to hepatic intoxication. Decholin may be given orally for prolonged effect, or may be administered intravenously as the sodium salt for prompt, intense action. Given by either route, profuse cholerisis usually follows.

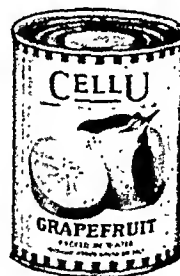
**Riedel-de Haen, Inc.**  
105 Hudson Street New York



# Decholin

## CELLU Canned Fruits

Packed in water without added sugar



### Carbohydrate Values

|                        |     |
|------------------------|-----|
| Applesauce             | 9%  |
| Apricots               | 7%  |
| Blackberries           | 7%  |
| Cherries (Red Pitted)  | 10% |
| Cherries (Royal Anne)  | 9%  |
| Grapefruit             | 8%  |
| Loganberries           | 7%  |
| Peaches (Yellow Cling) | 6%  |
| Pears (Bartlett)       | 6%  |
| Pineapple (Sliced)     | 12% |
| Prune Plums            | 9%  |
| Raspberries (Black)    | 9%  |
| Raspberries (Red)      | 7%  |
| Strawberries           | 6%  |
| Fruit Combination      | 9%  |

Increase the choice of fruit in the low carbohydrate diet

### FOOD VALUE

Fruits packed in water without added sugar are shown by chemical analysis to have their carbohydrate content reduced from that of the fresh product. Lessening the carbohydrate content makes it possible to include these fruits in diets where fresh fruits might be prohibitive. We list the carbohydrate values of Cellu fruits here for convenience of comparison.

### CONVENIENT TO USE

Cellu Canned Fruits not only increase the variety in the menu but add much to the convenience of food preparation. Saccharine may be added to these fruits if desired.

Send for Catalogue for Complete Information

Pin to your letterhead and mail

Send me your new catalogue which contains a complete description of  
Cellu Canned Fruits.

D. D. N. 9-35



**CHICAGO DIETETIC SUPPLY HOUSE**  
1750 W. VAN BUREN ST. CHICAGO, ILLINOIS

# AMERICAN JOURNAL OF DIGESTIVE DISEASES AND NUTRITION

The Official Publication of  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTENTS

### SECTION I—CLINICAL MEDICINE

|                                                                                                                                                                                                                                         | Page |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| ACUTE PANCREATITIS: A CLINICAL AND PATHOLOGICAL STUDY, WITH PERSONAL OBSERVATIONS— <i>Albert Le Sage, M.D., F.R.C.P., and Jean R. A. Le Sage, B.A., M.D.</i> - - - - -                                                                  | 449  |
| BACTERIOLOGICAL OBSERVATIONS IN DISEASE OF THE BILIARY TRACT: A COMPARISON OF OPERATIVE FINDINGS WITH THOSE OF NON-SURGICAL DRAINAGE OF THE BILIARY TRACT IN 104 CASES— <i>Eilif Hanssen, M.D., and Antony Yurevich, M.D.</i> - - - - - | 460  |
| CALCULATING THE DIAGNOSTIC VALUE OF GASTRIC ANALYSIS: A STUDY IN THE METHODOLOGY OF DIAGNOSIS— <i>Frances R. Vanzant, M.D., and Walter C. Alvarez, M.D.</i> - - - - -                                                                   | 466  |

### SECTION III—NUTRITION

|                                                                                                   |     |
|---------------------------------------------------------------------------------------------------|-----|
| A YEAR'S EXCLUSIVE MEAT DIET AND SEVEN YEARS LATER— <i>Clarence W. Lieb, A.M., M.D.</i> - - - - - | 473 |
| ABSTRACTS - - - - -                                                                               | 475 |

### SECTION V—THERAPEUTICS

|                                                                            |     |
|----------------------------------------------------------------------------|-----|
| GASTRO-INTESTINAL DIETS— <i>Diet Manual Mount Sinai Hospital</i> - - - - - | 476 |
|----------------------------------------------------------------------------|-----|

### SECTION VI—ABDOMINAL SURGERY

|                                                                                                                                        |     |
|----------------------------------------------------------------------------------------------------------------------------------------|-----|
| GASTRO-INTESTINAL MANIFESTATIONS ACCOMPANYING DISEASES IN THE UPPER URINARY TRACT— <i>Benjamin S. Abeshouse, Ph.B., M.D.</i> - - - - - | 477 |
|----------------------------------------------------------------------------------------------------------------------------------------|-----|

### SECTION VIII—EDITORIAL

|                                                                |     |
|----------------------------------------------------------------|-----|
| PRESIDENT'S ADDRESS— <i>B. B. Vincent Lyon, M.D.</i> - - - - - | 495 |
|----------------------------------------------------------------|-----|

### SECTION X—AFTER "HOURS"

|                                                                          |     |
|--------------------------------------------------------------------------|-----|
| MEMBERS OF THE JOURNAL'S EDITORIAL COUNCIL RECEIVE HIGH HONORS - - - - - | 499 |
| ABSTRACTS - - - - -                                                      | 501 |

### SECTION XI—SOCIETIES, PROGRAMS AND PROCEEDINGS

|                                                              |     |
|--------------------------------------------------------------|-----|
| IN MEMORIAM: ALBERT BERNHEIM— <i>David Reisman</i> - - - - - | 502 |
|--------------------------------------------------------------|-----|

### SECTION XII—"THE CLINIC"

|                                                                                                                                            |     |
|--------------------------------------------------------------------------------------------------------------------------------------------|-----|
| BILATERAL MASSIVE SUPRARENAL HEMORRHAGE IN AN INSTANCE OF HYPERFUNCTION OF THE SUPRARENAL CORTEX— <i>Frank R. Finnegan, M.D.</i> - - - - - | 504 |
| ABSTRACTS - - - - -                                                                                                                        | 507 |

PUBLISHED MONTHLY BY THE SANDFIELD PUBLISHING CO.

# CANNED FOODS IN INFANT NUTRITION

## I. Evaporated Milk

No phase of human nutrition has been more intensively studied than has that of infant nutrition. As a result of numerous investigations, much valuable information concerning the nutritive requirements of infancy has been accumulated. In addition, the quantitative nutritive demands of early life have been established within reasonable limits.

Along with advances in our knowledge of the science of nutrition have come changes in the older ideas concerning infant feeding. It is now an accepted fact that properly modified cow's milk can successfully supplement breast milk—in fact, where necessity or expediency demands, cow's milk properly modified and properly supplemented, can meet

fully all nutritive requirements of infancy. As far as proper nutrition is concerned, the "bottled baby" of today starts on life's road with brighter prospects than did his fellow-being of a generation ago.

Evaporated milk is particularly well adapted to preparation of milk formulas for infant feeding. Numerous studies, laboratory and clinical, have demonstrated its nutritive values—ample practical medical experience has proven its worth in infant nutrition. From the wealth of available literature, we have selected the following concise summary which describes this canned food and outlines those characteristics by virtue of which it is held in such high esteem as an infant food (1).

### (1) J. Am. Med. Ass'n 97, 1890 (1931)

1. Evaporated milk is pure fresh cow's milk with approximately 60 per cent of the water removed by evaporation under reduced pressure.

2. Evaporated milk is equal to pasteurized milk in all important food values; it supplies those vitamins which milk can be depended on to supply and in practically equal quantity.

3. Evaporated milk is sterile and therefore is the safest milk obtainable; it cannot introduce pathogenic micro-organisms to induce diarrhea in infants.

4. Evaporated milk casein curd in the stomach has a finer granular and softer texture or structure than that produced from raw or pasteurized milk; it resembles in physical structure the curd of human milk.

5. The fat of evaporated milk because of the homogenization processing is more finely dispersed than the fat of ordinary milk and therefore it is more readily acted on by digestive enzymes.

6. Evaporated milk is more speedily digested than raw or pasteurized milk or milk boiled only a very short time.

7. Evaporated milk is usually less allergic than raw or pasteurized milk.

8. Evaporated milk is one of the most convenient and economical forms of milk for preparing infant feeding formulas.

9. Evaporated milk enables introduction of more milk in the diet because it is concentrated.

10. Evaporated milk is considered by many pediatricians to be the best form of cow's milk for preparing the baby's formula.

• • •



The Seal of Acceptance denotes that the statements in this advertisement are acceptable to the Committee on Foods of the American Medical Association.

## AMERICAN CAN COMPANY

230 Park Avenue, New York City

# AMERICAN JOURNAL OF DIGESTIVE DISEASES AND NUTRITION

The Official Publication of  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTENTS

### SECTION I—CLINICAL MEDICINE

|                                                                                             |          |
|---------------------------------------------------------------------------------------------|----------|
| GALL STONES—A. J. Delario, M.D.                                                             | Page 511 |
| ABDOMINAL PAIN AS A MISLEADING SYMPTOM OF SPINAL CORD LESIONS—Everett D. Keifer, A.B., M.D. | 520      |
| ABSTRACTS                                                                                   | 526      |

### SECTION II—EXPERIMENTAL PHYSIOLOGY

|                                                                                              |          |
|----------------------------------------------------------------------------------------------|----------|
| THE AUTO REGULATION OF THE GASTRIC SECRETION—J. J. Day, M.D., and D. R. Webster, M.D., Ph.D. | Page 527 |
| ABSTRACTS                                                                                    | 531      |

### SECTION III—NUTRITION

|                                                                                                                                                                                                                                              |          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| INFLUENCE ON CARBOHYDRATE METABOLISM OF EXPERIMENTALLY INDUCED HEPATIC CHANGES. IV. BLOCK OF THE RETICULO-ENDOTHELIAL SYSTEM WITH SPECIAL REFERENCE TO THE KUPFFER CELL—T. L. Althausen, M.D.; B. E. Blomquist, M.A., and E. F. Whedon, M.S. | Page 532 |
| STUDIES ON CRYSTALLINE VITAMIN B <sub>1</sub> : OBSERVATIONS IN DIABETES—Martin G. Vorhaus, M.D.; Robert R. Williams, M.S., and Robert E. Waterman, B.S.                                                                                     | 541      |
| GASTRO-INTESTINAL MANIFESTATIONS OF HYPERINSULINISM—Seale Harris, M.D.                                                                                                                                                                       | 557      |
| ABSTRACTS                                                                                                                                                                                                                                    | 567      |

### SECTION V—THERAPEUTICS

|                                                                                                          |          |
|----------------------------------------------------------------------------------------------------------|----------|
| THE TREATMENT OF AMOEBIASIS WITH IODOXYQUINOLIN SULPHONIC ACID—F. W. O'Connor, M.R.C.S., and C. R. Hulse | Page 568 |
| ABSTRACTS                                                                                                | 569      |

### SECTION VII—SURGERY OF THE LOWER COLON AND RECTUM

|                                                                                              |          |
|----------------------------------------------------------------------------------------------|----------|
| THE SPECIFICITY OF THE FREI TEST IN LYMPHOPATHIA VENERA—Harry E. Bacon, B.S., M.D., F.A.C.S. | Page 570 |
| ABSTRACTS                                                                                    | 574      |

### SECTION VIII—EDITORIAL

|                                                   |          |
|---------------------------------------------------|----------|
| THE DIAGNOSIS OF GASTRITIS—George Eusterman, M.D. | Page 575 |
|---------------------------------------------------|----------|

### SECTION IX—BOOK REVIEWS

|                                                                                    |          |
|------------------------------------------------------------------------------------|----------|
| TRAITE DE GASTROSCOPIE ET DE PATHOLOGIE ENDOSCOPIQUE DE L'ESTOMAC—Francois Moutier | Page 576 |
| AN ATLAS ON BILIARY DRAINAGE MICROSCOPY—B. B. Vincent Lyon, M.D.                   | 578      |

### SECTION XI—SOCIETIES, PROGRAMS AND PROCEEDINGS

|                                                                                                                   |          |
|-------------------------------------------------------------------------------------------------------------------|----------|
| REPORT ON THE FIRST INTERNATIONAL CONGRESS OF GASTRO-ENTEROLOGY HELD AT BRUSSELS, BELGIUM — Anthony Bassler, M.D. | Page 581 |
| DELEGATES ON THE PART OF THE UNITED STATES TO THE FIRST INTERNATIONAL CONGRESS OF GASTRO-ENTEROLOGY               | 583      |
| REPORT ON THE ANNUAL SESSION OF THE AMERICAN PROCTOLOGIC SOCIETY—Curtice Rosser, M.D.                             | 584      |
| ABSTRACTS                                                                                                         | 584      |

### SECTION XII—"THE CLINIC"

|                                                                                                        |          |
|--------------------------------------------------------------------------------------------------------|----------|
| UNUSUAL CAUSES FOR SYMPTOMS OF BILIARY TRACT DISEASE, WITH CASE REPORTS—J. W. Thompson, M.D., F.A.C.S. | Page 588 |
| ABSTRACTS                                                                                              | 592      |

PUBLISHED MONTHLY BY THE SANDFIELD PUBLISHING CO.



# ELI LILLY AND COMPANY

FOUNDED 1876

*Makers of Medicinal Products*



Those coveted hours of repose, that desired serenity which the sleepless so envy in the more fortunate, are available to your patients through the use of Tablets Amytal. Ordinary hypnotic doses produce little or no demonstrable effect on blood pressure or respiration. Amytal augments the action of analgesics.

*Prompt Attention Given to Professional Inquiries*

PRINCIPAL OFFICES AND LABORATORIES, INDIANAPOLIS, INDIANA, U. S. A.

# AMERICAN JOURNAL OF DIGESTIVE DISEASES AND NUTRITION

The Official Publication of  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTENTS

|                                                                                                                                                                                                                                                                             | Page |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| SECTION I—CLINICAL MEDICINE                                                                                                                                                                                                                                                 |      |
| THE EXPERIMENTAL STUDY OF VISCERAL DISEASE— <i>Dr. Martin E. Rehfuess and Dr. Guy M. Nelson</i>                                                                                                                                                                             | 593  |
| ABSTRACTS                                                                                                                                                                                                                                                                   | 598  |
| SECTION II—EXPERIMENTAL PHYSIOLOGY                                                                                                                                                                                                                                          |      |
| THE CAUSE OF THE FAULTY DIGESTION IN DOGS WITHOUT STOMACHS— <i>Edward S. Emery, Jr., M.D.</i>                                                                                                                                                                               | 599  |
| EXPERIMENTAL STUDIES IN GASTRIC PHYSIOLOGY IN MAN: THE MECHANISM OF GASTRIC EVACUATION AFTER PARTIAL GASTRECTOMY AS DEMONSTRATED ROENTGENOLOGICALLY— <i>Harry Shay, M.D., and J. Gershon-Cohen, M.D., M.Sc. (Med.)</i>                                                      | 608  |
| ABSTRACTS                                                                                                                                                                                                                                                                   | 613  |
| SECTION III—NUTRITION                                                                                                                                                                                                                                                       |      |
| PRESENT CONCEPTIONS OF CALCIUM METABOLISM— <i>David Landsborough Thomson</i>                                                                                                                                                                                                | 614  |
| ABSTRACTS                                                                                                                                                                                                                                                                   | 617  |
| SECTION IV—ROENTGENOLOGY                                                                                                                                                                                                                                                    |      |
| THE ROLE OF VITAMIN B <sub>1</sub> IN TONUS OF THE LARGE INTESTINE— <i>M. I. Sparks, M.D., and E. N. Collins, M.D.</i>                                                                                                                                                      | 618  |
| SECTION V—THERAPEUTICS                                                                                                                                                                                                                                                      |      |
| COLON BACILLUS VACCINE THERAPY AS RELATED TO CHRONIC FUNCTIONAL DIARRHEA, CHRONIC HEADACHE, CHRONIC 'TOXIC VERTIGO' AND 'UNSTABLE' COLON (NON-ULCERATIVE COLITIS)— <i>John G. Matcer, M.D., James I. Baltz, M.D., James Fitzgerald, M.D., and Harris L. Woodburne, M.D.</i> | 621  |
| ABSTRACTS                                                                                                                                                                                                                                                                   | 629  |
| SECTION VI—ABDOMINAL SURGERY                                                                                                                                                                                                                                                |      |
| ASEPTIC ELECTROSURGICAL ENTEROSTOMY: A NEW METHOD— <i>Lester R. Whitaker, M.D.</i>                                                                                                                                                                                          | 630  |
| SECTION VII—SURGERY OF THE LOWER COLON AND RECTUM                                                                                                                                                                                                                           |      |
| THE HAEMORRHOIDAL LESION: ITS RADICAL CURE BY SUBMUCOUS INJECTION WITH OR WITHOUT THE LIGATURE OPERATION— <i>E. A. Daniels, M.Sc., M.D.</i>                                                                                                                                 | 631  |
| SECTION VIII—EDITORIAL                                                                                                                                                                                                                                                      |      |
| ON THE PROPOSED "INSTITUTE FOR GASTRO-ENTEROLOGICAL RESEARCH"— <i>Frank Smithies, M.D.</i>                                                                                                                                                                                  | 634  |
| PROCTOLOGY, A SPECIALITY, AND ITS INFLUENCE UPON THIS JOURNAL'S PUBLICATION POLICY— <i>Frank Smithies, M.D.</i>                                                                                                                                                             | 635  |
| ABSTRACTS                                                                                                                                                                                                                                                                   | 637  |
| SECTION IX—BOOK REVIEWS                                                                                                                                                                                                                                                     |      |
| VEGETABLES AND THEIR SIGNIFICANCE IN THE PHYSIOLOGY OF DIGESTION— <i>Dr. N. T. Leporsky</i>                                                                                                                                                                                 | 638  |
| CHILD PSYCHIATRY— <i>Leo Kanner, M.D.</i>                                                                                                                                                                                                                                   | 639  |
| ABSTRACTS                                                                                                                                                                                                                                                                   | 640  |
| SECTION XII—"THE CLINIC"                                                                                                                                                                                                                                                    |      |
| LARGE EPIPHRERIC DIVERTICULUM OF THE ESOPHAGUS— <i>B. D. Rosenak, M.D.</i>                                                                                                                                                                                                  | 642  |
| ABSTRACTS                                                                                                                                                                                                                                                                   | 645  |

PUBLISHED MONTHLY BY THE SANDFIELD PUBLISHING CO.

# ON THE PAGES OF THIS JOURNAL

we have, during the past year, presented for your consideration the qualities of Irradiated Pet Milk which have proved it to be a valuable aid in the treatment of gastro-intestinal disorders.

Physicians who have considered these qualities and who have put Pet Milk to practical test have been convinced that it serves remarkably well in the therapeutic procedures in which milk is employed.

For the convenience of physicians who may not have given consideration to the use of Pet Milk, we present a summary of its outstanding qualities:

**1**—Pure, whole cow's milk concentrated to uniform double-richness—a quality which facilitates the inclusion of more milk in the diet.

**2**—Free from all bacterial life—a safeguard against illness or intestinal irritation from this source.

**3**—Readily digestible, because of the formation of small, soft, non-irritating curds.

**4**—Especially suitable for the patient in whom milk causes allergic reactions—the advantage being due to alteration of the whey proteins.

**5**—Irradiated with ultra-violet rays, it contains appreciably more vitamin D than ordinary milk.

**6**—Costs less than other forms of milk, often only half as much as bottled milk.

We should be glad to send samples for trial purposes, and literature containing additional information.



PET MILK COMPANY, 1446L Arcade Bldg., St. Louis, Mo.

*Please send me, free of charge,*

- ☐ Samples Irradiated Pet Milk  
☐ Book of Recipes Rich in Milk

- ☐ Booklet for physicians  
☐ Reports of scientific studies

Dr. \_\_\_\_\_ Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_

(Attach your prescription form or letterhead to this coupon. Offer limited to physicians of Continental U. S.)

# AMERICAN JOURNAL OF DIGESTIVE DISEASES AND NUTRITION

The Official Publication of  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTENTS

JAN 31 1936

### SECTION I—CLINICAL MEDICINE

|                                                                                                                                                                                                   |          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| PSYCHOGENIC FACTORS IN ULCERATIVE COLITIS— <i>Arthur J. Sullivan, M.D.</i>                                                                                                                        | Page 651 |
| GASTROSCOPY WITH A FLEXIBLE GASTROSCOPE— <i>Rudolf Schindler, M.D.</i>                                                                                                                            | 656      |
| BACTERIOLOGICAL FINDINGS IN DISEASE OF THE BILIARY TRACT: AN IMPROVED METHOD OF OBTAINING CULTURES OF BILE BY DUODENAL DRAINAGE— <i>John Russell Twiss, M.D., and Charlotte H. Phillips, M.D.</i> | 663      |
| ABSTRACTS                                                                                                                                                                                         | 667      |

### SECTION II—EXPERIMENTAL PHYSIOLOGY

|                                                                                                                                                                      |     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| V. THE EFFECTS OF DRUGS ON THE MOTILITY OF ISOLATED SEGMENTS OF THE INTESTINE OF MAN— <i>J. Arnold Bergen, M.D., and John S. Guthrie, M.D.</i>                       | 668 |
| SOME NORMAL VARIATIONS IN THE EMPTYING-TIME OF THE HUMAN STOMACH (USING A CARBOHYDRATE MEAL)— <i>Edward J. Van Lier, Ph.D., M.D., and Carl K. Sleeth, A.B., B.S.</i> | 671 |
| ABSTRACTS                                                                                                                                                            | 672 |

### SECTION VI—ABDOMINAL SURGERY

|                                                                                                         |     |
|---------------------------------------------------------------------------------------------------------|-----|
| EXPERIENCES WITH POSTOPERATIVE JEJUNAL ULCER AND GASTROJEJUNOCOLIC FISTULA— <i>Frank H. Lahcy, M.D.</i> | 673 |
| ABSTRACTS                                                                                               | 677 |

### SECTION VII—SURGERY OF THE LOWER COLON AND RECTUM

|                                                                                                          |     |
|----------------------------------------------------------------------------------------------------------|-----|
| TRAUMAS RESULTING FROM SIGMOID MANIPULATION— <i>Burrill B. Crohn, M.D., and Bernard D. Rosenak, M.D.</i> | 678 |
| ANNUAL ABSTRACTS OF PROCTOLOGIC LITERATURE— <i>Clement L. Martin, M.D.</i>                               | 682 |

### SECTION VIII—EDITORIAL

|                                                                                           |     |
|-------------------------------------------------------------------------------------------|-----|
| THE GREAT VALUE OF SOME PHYSIOLOGICAL OBSERVATIONS ON MAN— <i>Walter C. Alvarez, M.D.</i> | 683 |
| THE ETIOLOGY OF PEPTIC ULCER: A REVIEW OF ONE THEORY— <i>Maurice B. Bonta, M.D.</i>       | 683 |

### SECTION IX—BOOK REVIEWS

|                                                          |     |
|----------------------------------------------------------|-----|
| THE MANAGEMENT OF COLITIS— <i>J. Arnold Bergen, M.D.</i> | 685 |
|----------------------------------------------------------|-----|

### SECTION X—AFTER "HOURS"

|                                                                                                                     |     |
|---------------------------------------------------------------------------------------------------------------------|-----|
| SOME SOCIAL AND MEDICAL IMPRESSIONS OF MOSCOW— <i>Charles Gordon Heyd, B.A., M.D., F.A.C.S.</i>                     | 686 |
| THE FIFTEENTH INTERNATIONAL PHYSIOLOGICAL CONGRESS, LENINGRAD AND MOSCOW, AUGUST 8-18, 1935— <i>A. C. Ivy, M.D.</i> | 692 |
| ABSTRACTS                                                                                                           | 696 |

### SECTION XII—"THE CLINIC"

|                                                                                                           |     |
|-----------------------------------------------------------------------------------------------------------|-----|
| A CASE OF NOMA (CANCER ORIS) COMPLICATING NON-SPECIFIC ULCERATIVE COLITIS— <i>Joseph S. Diamond, M.D.</i> | 698 |
| ABSTRACTS                                                                                                 | 706 |

PUBLISHED MONTHLY BY THE SANDFIELD PUBLISHING CO.

# The **Larostidin treatment**

## OF PEPTIC ULCER YIELDS EXCEPTIONALLY GOOD RESULTS

Four out of five cases, if put on the Larostidin treatment right away, will not have to be subjected to alkali medication or dietetic restriction.

*This is what you can confidently expect Larostidin to do for a gastro duodenal ulcer patient:*

- no interference with business or social duties
- freedom from all other medication
- relief of pain within a few days
- freedom from other symptoms in one week
- tolerance for regular diet in 5 to 10 days
- in most cases, a substantial gain in weight.

The evidence in favor of Larostidin should make it the first thought in peptic ulcer. No other treatment offers all these advantages.

*Issued in: Ampuls, 5 cc. Cartons of six (6)*

**HOFFMANN-LA ROCHE, Inc.**  
Roche Park • Nutley • N. J.

### THE EVIDENCE HAS PILED UP

During the last 12 months at least 58 articles on the Larostidin treatment of peptic ulcer appeared in the medical literature. The leading articles in British and American Journals were:

Bulmer, E.: *The Lancet*, 1931, 2: p. 1276-1278.

Volini, I. F. and McLaughlin, R. F.: *The Medical Record*, 1935, 141: 364.

Smith: *The British Medical Journal*, 1935, No. 3890, p. 154-159.

Craig: *The British Medical Journal*, 1935, No. 3896, p. 478.

Ryan: *The British Medical Journal*, 1935, No. 3899, p. 602-603.

Eads: *American Journal of Digestive Diseases and Nutrition*, 1935, 11: 426.

Rafsky: *Medical Record*, 1935, 142: 289.

Ahl: *The Military Surgeon*, 1935, 77: 216.

Physicians are invited to ask for a complete bibliography.

# AMERICAN JOURNAL OF DIGESTIVE DISEASES AND NUTRITION

The Official Publication of  
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

## CONTENTS

### SECTION I—CLINICAL MEDICINE

|                                                                                                                                                                                 | Page |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| THE INCIDENCE AND BIOLOGICAL CHARACTERISTICS OF THE HEMOLYTIC BACILLUS COLI IN THE INTESTINAL TRACT OF PATIENTS WITH CHRONIC ULCERATIVE COLITIS— <i>Edith E. Nicholls, M.D.</i> | 709  |
| THE TAKATA-ARA TEST OF LIVER FUNCTION— <i>Thomas B. Magath, M.D.</i>                                                                                                            | 713  |
| THE HIPPURIC ACID TEST FOR HEPATIC FUNCTION; ITS RELATION TO OTHER TESTS IN GENERAL USE— <i>Albert M. Snell, M.D., and John E. Plunkett, M.D.</i>                               | 716  |
| PHENOLPHTHALEIN STUDIES: I. COLLOIDAL PHENOLPHTHALEIN— <i>Bernard Fantus, M.D., and J. M. Duniewicz</i>                                                                         | 721  |
| ABSTRACTS                                                                                                                                                                       | 724  |

### SECTION II—EXPERIMENTAL PHYSIOLOGY

|                                                                                                                          |     |
|--------------------------------------------------------------------------------------------------------------------------|-----|
| THE INFLUENCE OF SOME ORGANIC AND INORGANIC ACIDS ON THE MOTILITY OF THE SMALL INTESTINE— <i>N. M. Gray, M.D., M.Sc.</i> | 725 |
|--------------------------------------------------------------------------------------------------------------------------|-----|

### SECTION III—NUTRITION

|                                                                             |     |
|-----------------------------------------------------------------------------|-----|
| BLOOD BUFFER VALUES IN MINERAL DEFICIENCY— <i>I. Newton Kugelmass, M.D.</i> | 730 |
| STATEMENT— <i>Clarence W. Lieb, A.M., M.D.</i>                              | 732 |

### SECTION V—THERAPEUTICS

|                                                                                                                                                           |     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| A NEW TECHNIQUE FOR THE CONTINUOUS CONTROL OF ACIDITY IN PEPTIC ULCER BY THE ALUMINUM HYDROXIDE DRIP— <i>E. E. Woldman, M.D., and V. C. Rowland, M.D.</i> | 733 |
| THERAPY OF PEPTIC ULCER: CONSERVATIVE VERSUS RADICAL— <i>Ernest H. Gaither, M.D.</i>                                                                      | 736 |

### SECTION VII—SURGERY OF THE LOWER COLON AND RECTUM

|                                                                                                                |     |
|----------------------------------------------------------------------------------------------------------------|-----|
| LYMPHOPATHIA VENEREA: A CLINICAL SURVEY— <i>Collier F. Martin, M.D., F.A.C.S.</i>                              | 741 |
| RECTO-URETHRAL FISTULA: AN OPERATION FOR ITS CURE— <i>Cecil D. Gaston, M.D., F.A.C.S., and A. B. Lee, M.D.</i> | 744 |
| ANNUAL ABSTRACTS OF PROCTOLOGIC LITERATURE— <i>Clement L. Martin, M.D.</i>                                     | 746 |

### SECTION VIII—EDITORIAL

|                                                                                        |     |
|----------------------------------------------------------------------------------------|-----|
| THE JOURNAL'S SECOND BIRTHDAY— <i>Beaumont S. Cornell, M.D., F.A.C.S.</i>              | 747 |
| REGARDING THE "HOUSE" PAGE AND CERTAIN EDITORIAL PROBLEMS— <i>Frank Smithies, M.D.</i> | 747 |

### SECTION IX—BOOK REVIEWS

|                                                                             |     |
|-----------------------------------------------------------------------------|-----|
| AIDS IN DIMINISHING OPERATIVE RISK— <i>Depuy de Frenelle</i>                | 749 |
| DIETETICS FOR THE CLINICIAN: SECOND EDITION— <i>Milton Arlander Bridges</i> | 750 |

### SECTION X—AFTER "HOURS"

|                                                                     |     |
|---------------------------------------------------------------------|-----|
| JOHANN GREGOR MENDEL— <i>J. Duffy Hancock, M.S., M.D., F.A.C.S.</i> | 750 |
|---------------------------------------------------------------------|-----|

### SECTION XI—SOCIETIES, PROGRAMS AND PROCEEDINGS

|                                                                                                  |     |
|--------------------------------------------------------------------------------------------------|-----|
| ANNUAL SESSION OF THE AMERICAN COLLEGE OF PHYSICIANS— <i>E. R. Loveland, Executive Secretary</i> | 755 |
| ABSTRACTS                                                                                        | 755 |

### SECTION XII—"THE CLINIC"

|                                                                                                            |     |
|------------------------------------------------------------------------------------------------------------|-----|
| SPONTANEOUS GASTRO-COLIC FISTULA— <i>Milton R. Louria, M.D., and Emil Rothstein, M.D.</i>                  | 756 |
| UROGENITAL SYMPTOMS REFERABLE TO INTRA-ABDOMINAL DISEASE— <i>Charles Gordon Heyd, B.A., M.D., F.A.C.S.</i> | 758 |
| ABSTRACTS                                                                                                  | 762 |

(INDEX NUMBER)

PUBLISHED MONTHLY BY THE SANDFIELD PUBLISHING CO.

# CANNED FOODS AND THE PUBLIC HEALTH

## I. The "Ptomaines"

• Many requests received for further information on canned foods have inquired as to some of the public health aspects of this class of foods. We appreciate the frank interest of our readers in this subject about which so much misinformation exists. We are glad, therefore, to devote this discussion, as well as subsequent ones, to the most popular of the lay misconceptions concerning the wholesomeness of commercially canned foods.

Some laymen hold the belief that canned foods, in some mysterious manner, develop "deadly ptomaines" within the can and hence the consumer of such foods stands in danger of "ptomaine poisoning". In the light of modern knowledge, this belief is ludicrous; it probably had its origin in the old "ptomaine theory" of food poisoning, now so thoroughly discredited by modern medical authorities (1).

Between the years 1870 and 1880, a large number of substances were obtained from protein material which had undergone bacterial putrefaction. These substances were aptly called "ptomaines", from the Greek "ptoma" or "dead body". Toxicologists of the day ascribed marked toxic properties to the new found ptomaines, chiefly by injection studies rather than by feeding tests.

The science of bacteriology was then in its

infancy—the true causes of food infection or intoxications were not known. Consequently, the discovery of the ptomaines, with their alleged toxic properties, permitted the convenient diagnosis of "ptomaine poisoning" for all illnesses following the ingestion of foods. Today, we know that such illnesses usually result from the ingestion of food which had been infected by certain bacterial groups, and not from protein degeneration products such as ptomaines (2, 3).

One authority has stated that "ptomaine poisoning is a good term to forget" (4).

To this we might add that it would also be well to discard the old, unfounded belief that foods in the tin can develop substances hazardous to health.

Canned foods are merely selected foods which, after proper preparation, are sealed in hermetic tin containers and given a heat process calculated to destroy pathogenic and spoilage organisms which might be present on the raw foodstuff. The hermetic seal prevents future infection of the food by such organisms and insures its preservation and wholesomeness.

Such are the simple facts. The cooperation of the medical profession is earnestly solicited in combating the ludicrous, yet widespread, lay prejudice against commercially canned foods.

## AMERICAN CAN COMPANY

230 Park Avenue, New York City

(1) Journal American Medical Ass'n, 90, 459 and 1573 (1928).

(2) Food-Borne Infections and Intoxications, F. W. Tamm, Twin City Pub. Co., Champaign, Ill., 1923.

(3) Food Poisoning and Food-Borne Infections, E. G. Jordan, University of Chicago Press, 2nd Ed., 1929.

(4) Preventive Medicine and Hygiene, N. J. Rosenau, Appleton-Century, New York, 5th Ed. 1927, p. 668.

*This is the ninth in a series of monthly articles, which will summarize, for your convenience, the conclusions about canned foods which authorities in nutritional research have reached. We want to make this series valuable to you, and so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles.*



The Seal of Acceptance denotes that the statements in this advertisement are acceptable to the Committee on Foods of the American Medical Association.

# SECTION I—*Clinical Medicine: Diseases of Digestion*

## Diarrhea

By

JOHN L. KANTOR, M.D.  
NEW YORK CITY, NEW YORK

### DEFINITION

**D**IARRHEA is a clinical syndrome in which the stools, generally increased in frequency, lose their normal form and assume a mushy or watery consistency. The changed appearance of the dejecta is due to their increased fluid content resulting from insufficient water absorption, abnormal exudation from the bowel wall and hastened transport through the intestine. Accelerated passage through the distal colon is essential for the occurrence of diarrhea since increased motility in the upper bowel segments alone will not suffice for the production of this symptom. Such a "diarrhea without diarrhea" may actually occur in mild cases of simple colitis, and has even been described in cholera—so-called cholera sicca (Schmidt) (16).

### CLINICAL PICTURE

The number of stools varies from two or three a day to one every few minutes; the consistency from mushy to liquid. Admixtures of undigested food, mucus, blood, or pus may be present. Abdominal distress, cramps, and flatulence are common. Sooner or later, the rectum rebels and proctitis supervenes. The chief systemic manifestations of severe, *acute diarrheas* are rapid dehydration and a toxemia which may lead to collapse. *Chronic cases* are marked by gradual but no less profound nutritional disturbances. Among these are emaciation and anemia from loss of nutriment including vitamins, as well as skeletal changes (osteoporosis, deformity, dwarfism) from loss of calcium salts when steatorrhea is prominent.

### CLASSIFICATION

In the present state of our knowledge, it is impossible to offer an etiological classification of the diarrheas. All that can be attempted is a crude division into *functional* and *organic* groups, as indicated by Table I. The organic cases are characterized by the presence, the functional by the absence, of a demonstrable lesion of the intestinal mucosa. In organic diarrheas the stools contain pus, blood, infectious bacteria, or parasites; the mucosal lesions may be seen through the proctoscope; there may be anemia, fever, emaciation, dehydration or collapse. In the functional diarrheas these features are absent. However, two important points must be kept in mind, first, that

long-continued functional disorders may lead to organic changes, second, that even extensive lesions (ulcers, tumors) may be present without the occurrence of any diarrhea whatever.

### LOCATION OF INTESTINAL CHANGES

A word may be said as to the portion of the intestine involved in diarrhea. The rectum may be the seat of infection, ulceration, or neoplasm. The colon is involved in the dysenteries, in neoplasms, in idiopathic ulcerative colitis and in simple colonic instability. The small intestine is specifically involved in typhoid fever, in the bacillary dysenteries, including cholera, in tuberculosis, and in the regional inflammation described by Crohn (3). A non-specific affection of the small intestine is called an enteritis, but the alimentary canal on either side is usually involved as well, so that one really has to deal with a gastro-enteritis, or an entero-colitis, or in some cases with a gastro-enterocolitis. All these varieties seem to be more common in children. In such cases, it has been suggested that the inflammation may result from an increase in the virulence of microorganisms normally present but ordinarily harmless, or by the ascent of lower intestinal bacteria into the upper bowel with resulting "wall infection."

### INCIDENCE

The incidence of diarrhea varies greatly with general living conditions and particularly with the effectiveness of sanitation. Diarrheal diseases have long been dreaded as the scourge of armies. In our Civil War, the hospital admission rate was 876 per 1000, the death rate 10 per 1000. In the Spanish American War, the admission rate was 402, the death rate 2, while in the World War with little exposure, the rates for our troops were 35 and 0.1 per 1000 respectively. Unfortunately, correspondingly exact figures for the incidence of these diseases in civilian life are not available. However, the 1933 outbreak of amebiasis which originated in Chicago that summer resulted in some 800 cases reported throughout the country by the following February; and this year's epidemic of bacillary dysentery in the metropolitan area involved between 1500 and 2000 cases, according to some authorities.

It is well known that infants are more affected by diarrheal disease than adults and that the incidence of diarrhea in hospitals is different from that in pri-

\*Read at the Seventh Annual Graduate Fortnight of the New York Academy of Medicine, October 23, 1934.  
Submitted November 14, 1934.



TABLE I  
CLINICAL CLASSIFICATION OF DIARRHEAS

| <i>Functional</i>                                                     | <i>Organic</i>                                     |
|-----------------------------------------------------------------------|----------------------------------------------------|
| 1. Simple or environmental (foods, drugs, etc.)                       | 1. Toxic                                           |
| 2. Anaphylactic or allergic                                           | a. exogenous (heavy metals)                        |
| 3. Gastrogenous                                                       | b. endogenous (compensatory in late stage, sepsis) |
| a. achylia                                                            | 2. Infectious                                      |
| b. delayed gastric emptying                                           | a. specific or primary bacillary                   |
| 4. Putrefactive                                                       | 1. cholera                                         |
| 5. Fermentative                                                       | 2. dysentery                                       |
| 6. Endocrine                                                          | 3. tuberculosis                                    |
| a. thyroid                                                            | 4. typhoid                                         |
| b. adrenal                                                            | b. non-specific or secondary                       |
| 7. Pancreatic                                                         | 1. functional (late stages)                        |
| 8. Idiopathic steatorrhea (sprue, non-tropical sprue, celiac disease) | 2. infectious (late stages)                        |
| 9. Pellagra                                                           | 3. Parasitic                                       |
| 10. Compensatory                                                      | a. protozoal                                       |
| a. uremic                                                             | 1. amebic                                          |
| b. skin burns                                                         | 2. flagellate                                      |
| c. senile                                                             | b. metazoal (strongyloides)                        |
| 11. Malabsorption                                                     | 4. Neoplastic                                      |
| a. intestinal resections                                              | 5. Amyloid                                         |
| b. <i>tabes mesenterica</i>                                           | 6. Obscure                                         |
| 12. Colonic instability ("nervous diarrhea")                          | a. <i>colitis gravis</i> (idiopathic ulcerative)   |
|                                                                       | b. regional ileitis                                |

vate practice. It is regrettable that hospital statistics are so meager. Apparently, the only article of importance on this subject originating from a hospital experience was published 21 years ago by Richard Cabot and Haven Emerson (2). It is based on a post mortem and clinical study of 640 cases.

Statistics derived from the private practice of any one individual are notoriously personal and cannot be expected to apply too precisely to the experience of another physician. Yet there is a unity of viewpoint and a continuity of observation that may make their presentation of some interest to others. Thus, in an unselected series of 3880 private patients complaining of various digestive troubles during the past 18 years, I observed 390 cases of diarrhea, an incidence of 10 per cent, with a mortality of 2.5 per cent. The frequency of the various varieties is presented in Table II. In 12 cases, the type of diarrhea remained undeter-

ined. In this series there were no cases of pellagra or proven pancreatic insufficiency in the functional group, or of poisoning with heavy metals, of cholera or of typhoid in the organic varieties.

#### DIAGNOSIS

The diagnosis of diarrhea is made essentially from the stool examination, but it is supplemented by proctoscopy, roentgen investigation, and the usual methods of history-taking and physical examination.

A mere naked eye inspection of the stool suffices to show whether the dejecta consist entirely of fecal matter or whether various unnatural constituents are present. Mucus suggests irritation, pus inflammation, blood ulceration of the intestinal mucosa, whereas a copious watery flux implies a serious loss of tissue fluids through this semi-permeable membrane such as one encounters in the so-called compensatory diarrheas

TABLE II  
TYPES OF DIARRHEA IN 390 PRIVATE CASES

| <i>Functional</i>                           |     | <i>Organic</i>                   |    |
|---------------------------------------------|-----|----------------------------------|----|
| 1. Colonic instability ("nervous diarrhea") | 210 | 1. Idiopathic ulcerative colitis | 41 |
| 2. Gastrogenous                             | 70  | 2. Tuberculosis                  | 12 |
| 3. Simple or environmental                  | 22  | 3. Post-dysentery                | 10 |
| 4. Idiopathic steatorrhea                   | 5   | 4. Regional ileitis              | 5  |
| 5. Allergic                                 | 5   | 5. Carcinoma of rectum           | 4  |
| 6. Compensatory                             | 4   | 6. Acute bacillary dysentery (?) | 3  |
| 7. Malabsorption                            | 2   | 7. Amebic dysentery              | 3  |
| 8. Endocrine                                | 2   | 8. Rectal stricture              | 1  |
| 9. Putrefactive                             | 2   | 9. Amyloid disease               | 1  |
| 10. Fermentative                            | 2   | 10. Trichomonas                  | 1  |
|                                             | 324 |                                  | 81 |

Functional, 324; Organic, 81; Undetermined, 12; Total, 417; Counted twice, 27; Net total, 390.

or in cholera. All the dysenteries exhibit blood and mucus, but the typical amebic stool differs from that of bacillary dysentery in that the fecal element predominates in the former. The presence of undigested food suggests an enteritis.

Information may also be obtained from the smell of the dejecta. Intestinal dyspepsias of the putrefactive and of the fermentative types can be differentiated by the corresponding putrid or sour odors, pancreatic insufficiency can be diagnosed at a distance by the high and penetrating aroma of rancid putrefaction, whereas the diarrhea of uremia is said to be characterized by the familiar evidence of ammonia. On the other hand, the "rice water" stools of cholera are as odorless as the bland discharges of an ileostomy.

The demonstration of *excessive fat* in the feces is important in the diagnosis of the various forms of steatorrhea. The well known bulky gray and greasy stools of gross pancreatic disease are due to the enormous output of free fat in this condition. In sprue and celiac disease, the stools are more likely to be frothy or soapy in appearance, since the fat is not present in the neutral state but rather in the form of fatty acid crystals and soaps. A simple microscopic examination is helpful. A small amount of feces is mixed with 30% acetic acid on a slide under a cover slip and then heated until the soaps and crystals are melted. On cooling, these take the form of clumps or globules which may be readily stained with Soudan III and thus identified.

Laboratory examination is necessary for the identification of the specific dysenteries. However, the laboratory (i.e. the microscope) must be brought to the bedside for the demonstration of the motile forms of the *endameba histolytica*. The material examined may be obtained either from the stool itself in the form of a clump of blood-streaked mucus, or by scraping the ulcerated bowel mucosa directly under proctoscopic visualization. If the acute phase is over and constipation is present, a fresh fluid specimen may be obtained by saline catharsis. It should be noted that formed feces contain only the encysted forms of the parasite. Such stools may be transported long distances for examination, but for accuracy this investigation requires a specialized technique.

In the bacillary diarrheas bacteriologic studies are essential for the identification of the specific agents of cholera and the various forms of dysentery. Unfortunately, it requires considerable time for a complete bacteriologic diagnosis. However, the comma bacillus can be fairly well identified on smears, and Haughwaut (9) has suggested that a differential diagnosis between bacillary and protozoal dysentery can be made in the earliest stages by a rapid examination of the fixed and stained exudate from the intestine. Later in the course of the bacillary infections (that is after the first week) agglutinins appear in the blood and can be utilized as aids to positive diagnosis.

Bacteriologic examination is also necessary for purposes of epidemiologic information and control, in identifying the specific organisms (paratyphoid enteritides group, and certain staphylococci) now believed to be the etiologic factors in those cases of food poisoning (popularly called "ptomaine") which chiefly affect the alimentary tract (7,13).

Proctoscopic examination is of value in the demonstration of new growths, impactions, ulcerations and inflammatory conditions in the rectum and lower pelvic colon. Ulcerative colitis usually gives a fairly characteristic picture but unfortunately it cannot always be positively distinguished from amebic dysentery.

Roentgen examination serves to confirm the diagnosis and indicates the extent of the involvement in advanced (not early) ulcerative colitis. It is the best available method (though not pathognomonic) for the diagnosis of ileo-cecal tuberculosis and of regional (terminal) ileitis. It may also be of value, according to some authorities, in identifying the cecal involvement of amebic dysentery. The characteristic dilation of the colon in cases of idiopathic steatorrhea, a finding which has not been adequately stressed, can best be demonstrated by an opaque enema. The usefulness of the x-ray in impactions and neoplasms needs no emphasis. Studies of the unstable colon are best carried out by the roentgen method. For a complete roentgen investigation both the progress meal (especially the "nine-hour" observation) and the opaque enema are desirable.

Finally, the history and other general and special examinations of the patient should not be neglected. By these means one may obtain information as to exposure to epidemic diseases, the ingestion of spoiled food or of drugs or poisons, the occurrence of diarrhea in other members of the family, individual idiosyncrasies or allergic states, unbalanced, restricted or insufficient diets, low or absent gastric acidity, susceptibility to heat or chilling of the body, the existence of chronic illness such as Graves' disease or renal insufficiency, previous abdominal operations, the possible presence of intestinal new growth or fecal impaction, and other similar factors of etiologic, epidemiologic or diagnostic import.

## SPECIAL VARIETIES

### A. Functional

*Simple or environmental* diarrhea may occur in any normal individual whose intestine is exposed to some unusual irritant. The most common cause is food which is either too coarse, too cold, or laden with bacteria already described as responsible for food poisoning. Cathartics, fecal impactions, and chilling of the body surface\* (15) may be cited as other causes. Simple diarrheas are very common but the condition is so mild and shortlived that most cases probably never come to the doctor.

*Anaphylactic or allergic* diarrhea is not always easy to prove to one's satisfaction. We could be sure of only 5 cases. Some patients were sensitive to but one food, others to many. Fish and veal seemed responsible in two patients. Other protein offenders were oatmeal, eggs, eggplant, beets and bananas. Milk and corn raised havoc in so many varieties of diarrhea that they could hardly be regarded as specific in the allergic reaction.

*Gastrogenous* diarrhea is common, 68 of our cases belonging to this variety. Achlorhydria was present in 57 cases, delayed gastric emptying in 7, and malfunctioning gastroenterostomy in 4.

\*One of my patients who had been a British soldier stationed on the Island of Malta told me that the sentries were always changed as soon as the cold, damp sirocco wind came up from Africa in the afternoon in order that all hands might have an opportunity for a hasty visit to the latrine.

*Putrefactive and fermentative* diarrheas are probably associated with an enteritis and result from a "wall infection" as already suggested. Intestinal fermentation was originally described by Adolf Schmidt (16) as "Gährungs dyspepsie." In this country little attention was paid to this variety until the recent study by Althausen and his collaborators (1) on "Carbohydrate-intolerance and Intestinal Flora," in which 50 cases were reported. This is still a rather ill-defined group in my opinion and may ultimately prove to be not so far removed from the idiopathic steatorrheas to be described later.

*Endocrine* diarrheas may be due to overactivity of the thyroid or hypoactivity of the adrenal gland. In one patient, the diarrhea was so definitely menstrual as to suggest the possibility of a gonadal influence. Our experience with this group is unfortunately very limited.

*Idiopathic steatorrhea* (sprue, non-tropical sprue, celiac disease) is probably not so rare in this climate as has been supposed. Attention has recently been called to this fact, chiefly by the work of Holmes and Starr (10) of Chicago, Haas (8) of New York, and Hess Thaysen (18) of Copenhagen. Since free fat does not appear in the stools, but only fatty acids and soaps, the movements are not greasy as in pancreatic disease but are more likely to be frothy and acid in reaction, as in fermentative diarrhea.† There is an associated intolerance for starches, except banana starch for some unexplained reason. The co-existence of meteorism with diarrhea is a striking clinical characteristic of this disease. The excretion of increased amounts of soaps causes a steady drain of calcium salts with the result that nervous irritability increases and skeletal changes supervene. These latter may result in infantilism or bony deformities. In this way a distant resemblance to rickets is suggested. We have record of five probable cases of idiopathic steatorrhea. One of these patients died following hemorrhage from a duodenal ulcer.

*Pellagra* is not represented in this series. My only experience with the disease was a limited one in a Southern camp during the World War. The patients promptly recovered on a well-balanced diet. The disease is "endemic" where the diet is lacking in the specific pellagra-preventive (B<sub>3</sub> or G) vitamin found in meat, eggs, milk and yeast. In this locality one should be on the lookout for cases due to faulty absorption produced by intestinal strictures, new growths or other similar interfering factors.

*Compensatory* diarrheas are rare but interesting forms which are assumed to occur when the usual avenues of excreting metabolic or other toxins prove inadequate. Renal insufficiency, skin burns and the universal breakdown of senility are usually cited as causative factors. Thus, older clinicians (17) have reported cases in which diarrhea has acted as a safety valve in preventing an impending uremia. That the intestine actually can excrete large amounts of retained nitrogenous substances recently has been shown by Williams and Dick (19). Our four patients presumably belong to the senile group, inasmuch as no other cause for the diarrhea (except achylia in one instance) was apparent.

*Deficient* absorption from resection of the small intestine seemed to cause diarrhea in two patients. The condition appears to be self-limited in proportion to the capacity of the remaining bowel to compensate for the loss of absorbing membrane.

*Colonic instability*, so-called "nervous diarrhea," was by far the most common variety observed in this series (11). The 212 cases in this group exceeded all the other forms put together. The usual cause is autonomic or emotional instability, but vicious bowel habits, especially the cathartic habit, must be held responsible in many cases. Alternating constipation and diarrhea are a common complaint and the constant recurrence of this sequence well illustrates the abnormal excursion in autonomic imbalance from the extreme of spasticity on the one hand to that of irritability on the other.

### B. Diarrhea Due to Organic Lesions

*Toxic* diarrheas may result from exogenous or endogenous causes. Among the former is poisoning with heavy metals such as mercury, arsenic, lead and bismuth. During the vicarious excretion of these substances by the intestine, the mucosa undergoes ulceration. Endogenous causes are illustrated by the toxins of uremia, sepsis, and burns. Ulcerations have been described in these conditions. Toxic diarrheas are not represented in our series of cases.

*Infectious* diarrheas also fall into two classes, specific or primary, and non-specific or secondary. Among the former are the bacillary diarrheas. Tuberculosis was diagnosed in twelve cases, all with advanced pulmonary involvement. Three of these patients are known to have died. There is no instance of primary intestinal tuberculosis in this series. A diagnosis of acute dysentery was ventured in three cases all of which began with a bloody diarrhea and resolved spontaneously after a short course. Although unconfirmed bacteriologically, it was assumed that these were probably cases resembling the mild Sonn  infections recently described by Felsen (4, 5). A fourth case was that of an intern who was a victim of a hospital epidemic of paratyphoid.

Typhoid diarrheas are not included in this group, but are sufficiently familiar to the reader not to require description. Cholera is a disease not seen in these parts. The dramatic speed with which it strikes is well illustrated in an anecdote related by an officer of the U. S. Army, who in 1902 was stationed with an infantry regiment in Luzon, Philippine Islands. He was assigned as counsel to defend a military prisoner before a court marshal which was to convene at 1 P. M. on a given date. At 10 A. M. that morning, the officer interviewed his client who was apparently in good health. At about 10:30 this soldier and half his company came down with cholera. By 3 P. M. the soldier was dead. The mortality among those affected was 30%. The mode of infection in this instance was traced to the company cook who, finding the breakfast coffee too hot, cooled it off by diluting it with water from a nearby stream. The breakfast was served at 6:30 so that the incubation period in this case was 4 hours, and the total duration of the disease but a half day longer.

The second subgroup of infectious diarrheas is non-specific or secondary in nature. They are conceived as resulting from any long-continued functional

†The possible relationship of sprue to some of the so-called fermentative diarrheas already has been mentioned. One wonders how many of the latter have an associated steatorrhea as well. Further work along these lines is desirable.

or organic condition in which the dominant rôle is now played by a superimposed infection with the original factor either entirely eliminated or set well in the background. In this group have been included one case of rectal stricture, as well as nine cases of persistent diarrhea, now presumably non-specific. The latter gave a very clear history of previous attacks of bacillary dysentery in places where the disease is believed to be endemic. Thus, three patients contracted the infection in Russia, and one each in China, France (wartime), Greece, Spain, Peru and Georgia. Since, according to Felsen (6), the ulcers of bacillary dysentery heal by the formation of granular tissue *without* new gland restoration, it seems proper to class these cases with the organic group.

*Parasitic* diarrheas in this locality are mostly protozoal, and especially amebic. It should be kept in mind in this regard that not all cases of amebiasis show diarrhea; and the present "epidemic" has taught us that the disease may assume unusual forms, resembling appendicitis or even pneumonia. Three proven instances of amebic diarrhea occur in our series. One case presumably due to trichomonas is also included.

*Neoplasms* of the lower bowel, especially of the rectum, are at times associated with diarrheal discharges. The movements, however, are not primarily fecal, but represent blood, pus and tissue detritus.

*Amyloid* diarrhea is represented by one probable case in which the terminal phase of a long drawn-out post-partum sepsis was marked by a constant intestinal flux. Unfortunately, there was no opportunity to confirm the diagnosis post-mortem.

*Colitis gravis* (so-called "idiopathic ulcerative colitis") furnished the largest number (41) of organic cases in this series. Again, it should be mentioned that not all forms of this disease are accompanied by diarrhea. Clinically it has seemed helpful to distinguish such sub-varieties as ulcerative, purulent, polypoid and indurative. Skin, joint and mucosal complications are often troublesome. The course is characterized by remissions and exacerbations. Four of the cases in this series went on to a fatal termination.

*Regional ileitis* was accompanied by diarrhea in 5 cases. The diarrhea may originate in the involved terminal ileum, but it may also be caused by the colitis which seems so regularly to accompany this condition.

The "*undetermined*" group consists of 12 cases in all but one of which adequate study was not possible. The one exception was a case of long standing diarrhea in which every diagnostic test proved negative, including repeated search for amebae by expert protozoologists. Fortunately, however, the patient made a complete recovery after a course of anayodin.

## TREATMENT

### A. General

*Rest.* General body rest is the first measure to institute in the treatment of diarrhea.

*Diet.* (1) All foods and drinks should be served hot. Hot tea and hot fruit juices are usually well taken. (2) The Schmidt intestinal diet is the best regimen for all simple diarrheas. (3) Milk is not well borne in the majority of patients. (4) Meat is usually well tolerated. (5) Roughage must be avoided (no raw fruit or vegetables) and small feedings are better than are large ones. (6) Raw apples, in scraped

form, have been shown by Moro (14) to exert a specific effect on the diarrheas of children. (7) In grave cases, especially when food cannot be taken by mouth, the parenteral administration of fluids in adequate amounts is a life saving measure.

*Drugs.* Generally speaking, these are to be avoided as much as possible. (1) Castor oil may be given at the beginning of a diarrhea which is due to ingested irritants. In the specific dysenteries this drug is recommended as a detoxicant. (2) Bulky, inert chemicals such as bismuth subcarbonate, barium sulfate, and kaolin are used to coat inflamed mucosa and bring down bacteria by "adsorption." To be really effective, these drugs must be used in tablespoon doses. (3) Calcium salts, such as the carbonate or gluconate, may be prescribed to replace calcium loss and to lessen transudation. (4) In desperate cases, resort must be had to opium.

*Local treatment.* Colonic irrigations are not advocated as a routine. In rectal tenesmus, however, considerable relief may be obtained by irrigating the rectum with hot, bland fluids through a return flow rectal (not colonic) irrigator of the Kemp type.

### B. Special

*Simple or environmental* diarrhea. Most cases are self-limited. If the irritant is still believed to be present a quick purge may be administered.

*Anaphylactic* diarrhea. The situation is somewhat similar to the preceding except that the patient is already sensitized to some foreign protein. Treatment involves the identification and avoidance of, or immunization to, the offending material.

*Gastrogenous* diarrhea. When achlorhydria is present the diet should undergo appropriate modification and HCl therapy should be instituted. For the cases with delayed gastric emptying the stomach should be treated primarily. This usually involves feeding in proportion to the gastric emptying power, frequent aspirations of old residues followed by lavage, alkalies when indicated, and finally, gastroenterostomy in advanced cases.

*Putrefactive* diarrhea is treated by initial castor oil catharsis and by the exclusion of foods which introduce putrefactive material into the intestine. In practice this means the administration of a strict carbohydrate diet to which proteins are added very gradually. According to the literature (12), di-hydranol should be effective in this condition.

*Fermentative* diarrhea is treated on the opposite plan, with a regimen somewhat similar to that used in diabetes, except that all rough and raw foodstuffs are eliminated. Owing to the possible relation of this variety to sprue, some of the principles of treatment outlined under the latter head would seem applicable here as well.

*Endocrine* diarrheas. The diarrheas of both Addison's and Basedow's disease are said to be controlled by rectal injections of epinephrin. Twenty-five drops of the 1:1000 solution in 200 c.c. of water are recommended for this purpose.

*Pancreatic* diarrhea is controlled either by large doses of pancreatin powder (30 grains 3 times daily) or, this failing, by fresh pancreas obtained directly from the abattoir.

*Sprue, non-tropical sprue, and celiac disease.* The diet is most important. Whole milk, fat and carbohydrate must be completely eliminated at the beginning of most severe cases. Protein is well tolerated, as is protein milk. Bananas and banana powder and strawberries are exceptions to the general rule and can be taken in large amounts, sufficient to sustain life alone. As many as 12 bananas and 3 quarts of strawberries may be fed daily even to depleted patients. The building up of the diet requires great individualization and much patience. The danger lies in adding too many different articles too quickly. Vitamin therapy is stressed by the most recent investigations. Vitamin B<sub>12</sub> (G), found in liver, yeast, and wheat germ is utilized. The dosage, according to some, may have to exceed that necessary in pernicious anemia. If sufficient amounts cannot be given by mouth, liver extract must be administered parenterally. In addition to B<sub>12</sub>, vitamins A and D, found in cod liver oil, are recommended. For the anemia, large amounts of iron, and for the osteoporosis and nervous irritability, substantial doses of calcium may be required. In my opinion parathormone should be administered with caution in this condition.

*Pellagra.* A high protein diet with liberal intake of vitamin B<sub>3</sub> (G) is recommended for this disease.

*Colonic instability ("nervous diarrhea").* Only a comprehensive plan of management can be successful in these cases. Vicious bowel habits must be eradicated, normal colon function must be restored and the autonomic nervous instability of the patient controlled as far as possible by all the methods at our disposal, such as rest, relaxation, sedation and common sense psychotherapy.

*Compensatory diarrheas.* These should be encouraged, rather than suppressed, since the flux tends to prevent the development of grave complications. Only in case the diarrhea leads to a permanent secondary (inflammatory) intestinal derangement should control measures be instituted. Exactly the same principles apply to the management of the toxic diarrheas.

The *infectious diarrheas.* (a) *Cholera.* Prophylactic vaccination was tried out during the World War and is said to have been effective. Active treatment is directed toward overcoming the collapse associated with the rapid dehydration and toxemia. For this purpose, practically continuous inflow of fluids by vein and subcutaneously is essential. Rogers recommends a hypertonic solution of sodium, calcium, and potassium chloride intravenously and the frequent administration of potassium permanganate pills by mouth.

(b) *Bacillary dysenteries.* Fortunately, the grave Shiga type is not seen here. For this form, an antitoxic serum is available. The specific dysenteries which are likely to be encountered in this part of the world belong to the Flexner strain or to similar relatively mild organisms such as the Sonn . Specific bacteriophages are now available. Felsen prefers the rectal route of administration unless the diarrhea is too intense, when the intravenous method is required. This treatment is most likely to be efficacious in the first week of the disease. For elimination of the toxin, daily castor oil catharsis is recommended. Fluids must

be administered parenterally when necessary.

(c) *Tuberculous enteritis.* There is no specific treatment. Opium is required in the severe cases. Calcium gluconate intravenously may help some patients.

*Amebic dysentery.* Active treatment is based on the use of three drugs, ipecac, arsenic, iodine, in various forms and under various trade names. It is believed that ipecac attacks the parasites in the tissues, whereas the other two drugs kill the amebae on the intestinal surface. A fairly representative therapeutic program is as follows: (1) Emetine hydrochlorid 1 grain is given hypodermatically each day for 10 days, but not longer on account of the danger of toxicity. During the same period one 10 grain tablet of aluminum salicylate of ipecac ("alcresta") is given 3 times a day. (2) Next follows a week of rest and observation of the stools. (3) Following this comes a week of treatment with either arsenic or iodine. If the former is selected stovarsol (acetarson) is administered in the form of 0.25 gram tablets 3 times a day. If iodine is preferred anayodin (chiniofon) pills, 4 grains each, are given 3 times a day for 8 days, or in any other dosage till a total of 96 pills is taken. It should be mentioned that anayodin produces an initial diarrhea. These measures usually suffice. If amebae persist in the stools, the dose of anayodin should be cut in half and the drug administered by rectum. For this purpose 200 c.c. of a warm 2 per cent solution should be given as a retention enema each day for 10 days.

*Colitis gravis, idiopathic ulcerative colitis.* Since the etiology is undecided, a specific therapy is lacking. The importance of general supportive measures such as rest and adequate feeding is obvious. Much can be accomplished with diet in the suppurative variety (pus stools, fever). Here a strict protein regimen agrees best. The meals should be built up of meat, fowl, fish, sea food, eggs, gelatin, meat soups, tea and hot fruit juices. Butter is permitted and saccharin should be used for sweetening. After the stools become formed and the fever drops, various starches may be added, beginning with the finer processed flours such as Robinson's "patent barley."

In the hands of some careful observers, the use of autogenous sera in acute cases and of vaccines in the chronic stages gives good results. In our experience improvement and even remission may occasionally be obtained from the use of small (300 c.c.) whole blood transfusions. These may be repeated weekly for about 6 weeks.

As in all dehydrations liberal saline-glucose infusions are indicated. Opium is unavoidable in bad cases. Ileostomy may be tried but though it seems to give temporary relief, it does not prevent the progress of the disease with its numerous crippling complications. On the whole, the present treatment of this condition is far from satisfactory.

*Neitis.* For the cases seen to date, surgical therapy is indicated. The results are satisfactory.

## RECAPITULATION

This presentation may be condensed in the form of the following rough rules of procedure for the management of a case of diarrhea in this locality:

1. Decide whether the condition is functional or organic. Look at the stool. If blood is present the diarrhea is probably organic.

2. Make an immediate decision about the initial feeding plan. For mild or functional cases, prescribe the Schmidt diet without milk. For the more severe cases, give only hot fluids as tea or fruit juices, but avoid milk. In the still graver forms (in this locality chiefly in infants) maintain the tissue fluid level by parenteral saline-glucose injections.

3. In all recent, bloody diarrheas make an urgent differential diagnosis between amebiasis, bacillary dysentery and idiopathic ulcerative colitis. If the diarrhea has persisted for over two weeks, a bacillary origin can be regarded as the least likely of the three in this community.

4. If you have reason to suspect amebiasis in the acute phase, bring the microscope to the patient and not the stool to the laboratory. Scrapings of bowel wall through the proctoscope give the best material.

If the diarrhea has ceased, produce a watery stool with a saline laxative. Look for active amebae with typical pseudopodial movements. Do not waste time looking for cysts unless you are a first class protozoologist.

5. If you suspect bacillary diarrhea (in this locality) have the stools cultured in the first week and have the blood tested for immune bodies in the next two weeks. Later in the disease these tests are seldom worth the trouble.

6. After excluding the specific dysenteries you may proceed more leisurely to the diagnosis and treatment of the chronic functional and organic conditions.

7. In recurrent diarrheas, especially when alternating with constipation, remember the frequency of colonic instability and the importance of restoring normal bowel function.

8. In all obscure chronic diarrheas keep in mind the possibilities of achylia gastrica and idiopathic non-tropical sprue, and make appropriate diagnostic and therapeutic investigations.

## REFERENCES

1. Althausen, T. L., Gunnison, J. B., Marshall, M. S., Shipman, S. J. Carbohydrate Intolerance and Intestinal Flora. *Trans. American Gastro-Ent. Assoc.*, 1933.
2. Cabot, R. C., Emerson, H. Causes, Types, and Treatment of Diarrhea in Adult Life. *J. A. M. A.* 61: 1015, 1913.
3. Crohn, B. B., Ginzburg, L., Oppenheimer, G. C. Regional Ileitis: A Pathologic and Clinical Entity. *J. A. M. A.* 99: 1323-1329, 1932.
4. Felsen, J. Sonné Dysentery. *J. A. M. A.* 103: 966-971, 1934.
5. Felsen, J., Rundlett, E. V., Sullivan, J., Gorenberg, M. Atypical Flexner Dysentery: A Preliminary Report of the Jersey City Epidemic. *J. A. M. A.* 103: 1055-1058, 1934.
6. Felsen, J. A Practical Etiological, Pathological and Clinical Consideration of Intestinal Ulceration. *Am. J. Dig. Dis. and Nutr.* 1: 297-305, 1934.
7. Geiger, J. C., Gray, J. P. Food Poisoning. *J. A. M. A.* 101: 975-979, 1933.
8. Hnas, S. V. Celiac Disease. *J. A. M. A.* 99: 448-452, 1932.
9. Hauchwout, F. G. The Microscopic Diagnosis of the Dysenteries at Their Onset. *J. A. M. A.* 83: 1166-1160, 1924.
10. Holmes, W. H., Starr, P. A Nutritional Disturbance in Adults Resembling Celiac Disease and Sprue. *J. A. M. A.* 92: 975-980, 1929.
11. Kantor, J. L. The Unstable Colon. *South. M. J.* 25: 29-37, 1932.
12. Leonard, V., Feirer, W. A. Control of Intestinal Putrefaction in Man by Oral Administration of 2-4-dihydroxyphenyl n-heptane. *Bull. Johns Hopkins Hospital* 48: 25-38, 1931.
13. McBurney, R. Food Poisoning Due to Staphylococci. *J. A. M. A.* 100: 1999-2001, 1933.
14. Moro, E. Apple Diet for Treatment of Diarrheal Conditions in Children. *Abstr. J. A. M. A.* 94: 673-674, 1930.
15. Schmidt, Adolf. Ueber den Zusammenhang von gutartigen Durchfällen mit dem Genusse schwerverdaulicher Nahrung und mit Abkühlung des Bauches. *Med. Klin.* 11: 207-208, 1915.
16. Schmidt, A., Von Noorden, C. Klinik der Darmkrankheiten. Munich, Bergmann, 1921.
17. Stern, H. A. Consideration of the Compensatory Diarrheas. *J. A. M. A.* 51: 467-471, 1908.
18. Thaysen, T. E. H. Non-Tropical Sprue: A Study in Idiopathic Stenterria (in English). Copenhagen, Levin and Munksgaard, 1932.
19. Williams, J. L., Dick, G. F. The Excretion of Non-Protein Nitrogen Substances by the Intestine. *J. A. M. A.* 100: 484-487, 1933.

## Constipation

By

HENRY JAMES SPENCER, A.M., M.D.\*  
NEW YORK CITY, NEW YORK

**C**ONSTIPATION is a SYMPTOM and not a DISEASE.

A definition of constipation necessarily is rather elastic but it considers the elements of frequency of evacuation, volume, consistency and rate of transit through the intestines of the fecal mass. Fundamentally, constipation is undue and habitual delay in the evacuation of fecal wastes, but in defining the term "undue delay" again the factors of frequency of dis-

charge, volume, consistency and rate of transit must be observed and evaluated.

In order correctly to observe and evaluate these factors one must know something of the development, anatomy and physiology of the colon and other related parts and properly to deal with disturbed anatomy and physiology he must also know how the disturbing factors produce their effects. He then may hope to correct conditions and counteract factors which cause constipation. The following discussion is a brief presentation of the essential facts and some of the known disturbing factors including their mode of action.

\*Visiting Physician and Director, Second (Cornell University) Medical Division, Bellevue Hospital.  
Submitted November 5, 1931.



Finally suggestions are made regarding the correction of certain conditions and the combatting of others having to do with constipation.

### ANATOMIC CONSIDERATIONS

The colon is derived from the hind gut. At an early age the cecal bud appears at the junction of the small and the large intestine. Later it forms the cecum and the appendix. The whole gut lengthens, loops upon itself and undergoes a rotation which brings the colon into its well known, usual position. There is a concomitant descent of the cecum which usually (88%) carries it to the right iliac fossa. Both rotation of the colon and descent of the cecum may fail to occur. These facts account for abnormalities of location of the colon and of its relation to other viscera, some of which anomalies may promote constipation. At times the colon may lengthen to a degree where the length itself favors constipation.

The cecum is the widest part of the colon and its haustra are wide and shallow. It is separated from the ascending colon by an especially deep haustrum. The cecum and the descending colon muscularly are the weakest portions of the large intestine. The transverse colon exhibits the deepest haustra. The descending colon and the recto-sigmoid have the most powerful muscles. The fully developed colon ranges from 150-210 cm. (60-84 inches) in length. All measurements of length and diameter of intestines are approximate because the muscular tone constantly is changing and with it change the length and diameter of the organ. The capacity of the colon is between 1500 and 2500 cc.

The effective lumen of the colon roughly is about a third of its apparent cross-area, due to the transverse inter-saccular folds. Even this lumen is modified greatly by the tone of the musculature.

The passage of contents further is influenced by various structures along the bowel's course. The ileocecal sphincter or valve largely prevents the passage of material into the cecum when that segment is full; the valve is capable of preventing the passage of enema fluids into the ileum, though commonly it does so only partly.

The ceco-colic sphincter is a relatively constricted point between cecum and colon, due to the specially deep haustrum previously mentioned, which regulates the escape of cecal contents into the colon. This may be a factor in ileo-cecal stasis.

The colon's hepatic and splenic flexures are important divisional points.

The rectosigmoid's non-striated muscle-band narrows the junction of these portions and is located at a point where considerable angulation may take place, angulation which tends to slow the fecal stream.

The anal sphincters, internal and external, close the highly important terminus.

The mucosal folds and the *muscularis mucosae* form an active membrane with changing contours which must be regarded seriously when interpreting roentgenological silhouettes.

The position of the colon varies widely from the text-book standards of past generations. Thus, the cecum is in the iliac fossa in 85-90 per cent. of the

population and the lowest point of the transverse colon lies 3 to 4 inches below the inter-iliac line in about 40 per cent. of healthy college students. The hepatic and splenic flexures vary in position to an equally high degree and their positions (relative to each other in height) vary greatly. Today, functional efficiency assumes far greater significance than does anatomic position; in the great majority of patients the low and even the "pelvic" positions of these viscera usually bear no associated important functional relationships. Indeed, functional disturbances may occur when the viscera lie in the "text-book", presumably "normal" position. In general then the position of the viscera is not a factor indicative of function.

### COMPARATIVE ANATOMY

The human digestive tract is a compromise between those of the herbivorous and the carnivorous groups of animals; it has more of the characteristics of the carnivores as to length and more of the herbivores in respect to the cecum and the extent of sacculatation, although these features are far less developed than they are in true herbivores. The cecum and the sacculatation were developed for the long retention and thorough digestion and absorption of the celluloses. The herbivorous gut is 25 to 100 times the animal's body length, the carnivorous, 4 to 8 times and the human not over 8 or 9 times; in many instances less. These facts have real significance in the selection of the diet and the treatment of constipation.

### PHYSIOLOGY

The food which has been digested in the stomach and the upper segments of the small intestine, together with the water derived from the food and drink and such as is added in transit, normally arrive at the cecum in a soft, mixed, fluid state in from two to four hours; usually the mass has left the ileum in from four to six and one-half hours.

The gastrocolic reflex which is initiated by the ingestion of food and at times by the smell, sight or thought of it, results in the discharge of the ileal contents into the cecum.

The residue remains in the cecum and the ascending colon for the greater part of the time prior to defecation. Although most of a given "shipment" of food will be evacuated at one defecation, Alvarez has shown, by his experiments with beads, that a small part (about 15%) goes through quickly; the bulk, 50%, is passed on the second day; approximately four days are required to pass 75% of the mass. In Alvarez' studies, some individuals passed 85% in the first twenty-four hours and yet in some, nine days were required to evacuate 50-60%. Those subjects who passed most of the beads in twenty-four to forty-eight hours had accompanying soft, frothy, foul, incompletely digested food residues. The slower the passage the more formed and well digested were the stools. Probably we are correct in expecting food residues normally to pass through the alimentary tract in forty-eight to seventy-two hours and not faster. The normal stool probably is a cylindroid which shows neither fragmentation nor haustral markings, whose latter part is soft and tapering. It causes no pain or discomfort when passed.

In the colon, and particularly in the cecum and the ascending segment, churning of the mass occurs; and during this process the body retrieves the water. When the hepatic flexure is reached, the consistency of the mass has become definitely firmer. In the meantime, the cellulose has been subjected to bacterial action; it is claimed that this change permits considerable of it to be absorbed. End products of protein, fat and carbohydrate digestion are absorbed in appreciable amounts.

The material coming from the ileum seems to be pushed forward through the cecum and the ascending colon without noticeable peristaltic waves; it finally passes the hepatic flexure. In the transverse colon mass movements appear periodically; the haustrations in the transverse colon suddenly disappear; the fecal material agglomerates to form a cylindroid about 6 inches (15 cm.) long; then suddenly a contraction wave develops and the mass is driven beyond the splenic flexure into the descending colon, or perhaps as far as the recto-sphigmoid. This type of activity usually occurs five or six times daily.

In the rectum, the fecal mass arouses the rectal reflex or the "call to defecation". When this is responded to, the abdominal and recto-sigmoidal muscles become active, ably seconded by the levatores ani; the anal sphincters then relax and the fecal mass is expelled.

Frequently the entire mass as far back as the splenic flexure is evacuated at one defecation. Sometimes a shorter mass, that occupying the sigmoid and rectum only, is passed. Occasionally an even larger stool is produced.

The normal person usually passes several small or one large stool daily. When a very large stool is passed, it is noted that there may follow no call to defecation for two or three days or until a period when the colon again is sufficiently filled to arouse the defecation reflex.

Further important facts are those which Alvarez has disclosed in his "gradient theory" of the mechanics of the digestive tract. A gradient is a "state of affairs" in which there is a graduated change of some given attribute over a definite time or space. Thus a glass rod heated at one end has a gradient of temperature within the two ends. Alvarez has shown definite gradients in the mechanisms of movement in the esophagus, stomach, small intestines and colon. For example, in the small intestine he has demonstrated that there exists a higher rate of rhythmic contraction in the duodenum than in the terminal portion of the ileum. There is a gradual fall in the rhythmic rate as one proceeds from the jejunum to the ileum. Similarly, studies of muscle tonus, metabolic rate and irritability show that such are more marked at the duodenum than at any point caudad. As Alvarez expresses it "the rate of rhythmic contraction continues to vary inversely as the distance from the pylorus". He further says, "the direction of transport of material in a tubular organ depends upon the gradients of rhythmicity, tone and irritability". And again "the permanence of the gradient in the gut is to be expected". He illustrates the fundamental nature of the gradient by citing an experiment with dogs in which experiment when sections of the small intestine had

been cut free, they were turned end for end and in such abnormal relationship were anastomosed. Regular healing occurred. When roughage was eliminated from their diets, the dogs were kept alive for months. Finally, they died, because intestinal obstruction occurred at the proximal anastomosis; such obstructions were caused by bits of straw, bone, wood, etc. It was shown that the original direction of peristalsis remained fixed and that only liquids could be forced through the intestinal lumen.

A second very important point is that while stimulation of the intestinal wall at any point will cause a contraction wave to travel both up and down the tube, those waves traveling up soon are obscured while those downward bound keep traveling. The gradation in rhythmicity makes this possible.

Finally, if one stimulates the intestine at a point and produces a tonic contraction then from it the waves pass cephalad and caudad and if then one starts a second tonus ring caudad to the first, the waves reaching it from above are blocked. Alvarez translates this into the law that "stimulation at any point leads to the holding back of material coming from above and the hurrying on of material already below". Call to your mind this effect as seen in the digestive tract responses in acute appendicitis, namely, early nausea and vomiting and often sudden diarrhea.

It does not appear advisable to confuse the reader at this point by injecting the problem of reverse peristalsis although even this phenomenon is in keeping with the gradient theory. This is thoroughly discussed by Alvarez in his "The Mechanics of the Digestive Tract".

Behind all which we have mentioned about the "gradients" is the power of rhythmic contraction inherent in all contractile tissues, contractions which are dependent upon rhythmically recurring chemical cycles. The rhythmic rate seems dependent upon the inherent metabolic rate of the individual tissue concerned. Thus, heat which raises the metabolic rate increases the rate of rhythmic contraction of the contractile tissue under consideration whichever that tissue may be. This fact is borne out by the intestinal musculature whether it is part of the intact body or isolated for study in the physiological laboratory.

Since completely denervated intestinal muscle still contracts rhythmically it is presumed that the "contraction wave" arises in the muscle cell itself and is conducted by it and that the function of the nerve mechanism is to coordinate or speed up movements and govern muscle tonus. This point is opposed vigorously by many physiologists.

Increase in the tension within the lumen of the bowel stimulates contraction of the muscular coat of the bowel at the distended point. This contraction increases the tension in the adjacent tissue which in turn contracts and forms part of the advancing wave which develops.

The intestinal musculo-neural apparatus has characteristic peculiarities. The contractions are more sluggish than are those of striated muscle. The tonus and hence the length of the gut constantly are changing. Several successive stimuli make it refractory. A long rest leaves the bowel very react and a



it responds promptly and explosively to a slight stimulus. This is the condition of the tract in the normal person after a night's rest and seems to explain the high efficiency of the mechanism in bringing on a bowel movement immediately after breakfast. Another characteristic is the bowel's ability to maintain a firm and lasting contraction without fatigue, a condition seen especially in the colon.

Direct, constant irritation causes spasmodic contraction; thus, an ulcer near the cardia, pylorus, ileocecal valve or the anus may cause localized spasm. Carcinomata, because of their tendency to produce degenerative changes in the muscular tissue, do not stimulate powerful contractions of the muscles, hence very often they give rise to no symptoms until mechanically they produce obstruction. The sphincters being more irritable than is the adjacent gut (since they are compact collections of muscular tissue) respond, when the gut, generally, does not.

In the limited space allowed we must be content to point out that emotional states cause digestive tract atony or persistent spasm and hence play a very important part in causing constipation. The preceding speaker has covered this point most satisfactorily. The nerve pathways affecting the colon are so poorly understood that it is best to omit them from this discussion.

The colon does not show a rhythmic rate approaching that of the small intestine, and its irritability is considerably less. The blood supply to tissues roughly parallels their metabolic rate. In illustration of this statement, it is interesting to observe that the vascular network in the mesentery becomes less abundant as we pass from the jejunum to the colon. The colon has the least volume of blood supply of the entire alimentary tract, so limited in fact that surgical procedures are handicapped as a result.

Characteristic of the muscle of the colon is its sluggishness, its relatively slow rate of contraction, its pronounced tonus-waves and its tolerance of distension. It seems designed for holding material without vigorous peristalsis for hours. The descending colon and the sigmoid probably are more sensitive than is the remainder of the colon. At autopsy they usually are found empty. The irritability of the sigmoid probably keeps the fecal mass from "packing" against the sphincter and except at such times when the pressure from above is unusually great, as for example after a meal.

Apparently a filled cecum stops the opening of the ileocecal valve. The effect of direct stimulation of the cecal mucosa through a cecostomy wound, by acid, an electrode or by pinching, tends to retard material coming down from above.

#### PATHOLOGICAL PHYSIOLOGY

Thus far, the normal physiology alone has been discussed with the exception that the spasmodic contraction of the sphincters caused by the irritation of an ulcer was noted. With this information in mind we now shall present some situations which are known to occur with constipation.

In constipation, overactivity of the colon may occur; this may take the form of rapid reabsorption of water

with resultant drying and concentration of the feces; or the more correct conception of the situation may be that there is delay in the passage of the mass through the colon which allows a longer time for dehydration. In any case, the colon's contents increase in consistency as they pass from cecum to rectum so that even at the hepatic flexure, rounded masses already may have formed; if that takes place no churning of material is possible and the individual masses are pushed onward into the rectum like cars on a track.

A condition frequently associated with constipation and, at times probably responsible for it or aggravating its degree, is distension or flatulence.

There are three main sources of gas in the digestive tract: "swallowed" air, gas derived from food by fermentation or putrefaction and gas which is liberated from the blood stream.

Air may be swallowed as such or trapped in food or drink. Most swallowed air never reaches the stomach; if it does usually it is belched promptly. With cardio-spasm and postoperatively appreciable amounts of air may be retained and may be carried into the intestinal tract to the colon. Such an happening formerly, but erroneously, was given much weight because it was not appreciated that true colonic flatus contains much nitrogen. Swallowed air has slight significance compared to true flatulence.

Fermentation particularly, and putrefaction to a far less degree, may account for important amounts of gas. In the herbivora, fermentation is the chief and a very large source of intestinal gas, but in man usually it is not. Hyperchlorhydria, by causing marked softening of the cellulose in the diet and permitting more fermentation may account for considerable gas production. Stagnation in the cecum may be favorable to added fermentation but this very stagnation provides more time for passage of gas per rectum or for absorption in the blood. The relative importance of swallowed air and gas from fermentation as against blood-derived gas seems changed in the postoperative states and in ill persons confined to bed.

The chief source of gas usually is the blood. Without going into the technicalities of the laws governing gas exchange between tissues and blood, on the one hand, and blood and the pulmonary air on the other, suffice it to say that the same laws apply in gas exchange between the blood stream and the intestinal lumen. It is certain that active exchange of gases occurs between those in the blood and those in the intestine. The normal exchange leaves very little gas residue in the intestine after the usual amount of flatus is discharged. The gases present are exchanged at rates and in the directions which the laws concerning gas pressure determine. Thus, the diffusion constants for the gases, their ability to combine chemically with hemoglobin or to dissolve in the plasma and the relative tensions of the gases present in the intestine, the tissues, the blood and the surrounding air, all play a part in the process. Hydrogen disulphide, oxygen and carbon dioxide readily are removed from the colon; hydrogen and methane may be absorbed but while nitrogen, with which the blood and tissues are saturated, easily is discharged into the intestine it is absorbed into the blood and carried away with difficulty. This physico-chemical phenomenon and not

swallowed air probably in most instances explains the high nitrogen content of intestinal flatus.

In certain conditions, the preponderance of exchange being from the blood into the colon leads to distension of the gut. It is important that one appreciates this possibility, for distension thus derived may cause or aggravate constipation. It is evident that the management of distension requires a clear understanding of the mechanism of its production.

Hence, flatulence may occur if:

1. More than the normal volume of air is swallowed.
2. The intestinal stream is delayed (by psychic or nervous causes or by constipation).
3. Carbohydrate digestion is slow or incomplete and colonic fermentation thus has opportunity to develop.
4. Absorption of gas from the bowel into the blood is diminished due to congested mucosae, atonic gut or diminished intra-abdominal pressure.
5. Circulation is interfered with when mesenteric circulation is obstructed, especially on the venous side; the gas exchange is positive for the intestine; cardiac crises; paralytic ileus.
6. The gas carrying power of the blood is diminished (probably not significant).
7. Escape of gases in the lungs is diminished as in pneumonia.

Careful consideration of all these factors is necessary when serious bowel distension threatens or exists; the significant causative factors should be prevented or diverted so as to reduce distension. Thus, changes in the diet, measures to combat intestinal stasis or to improve the circulation, treatment of disturbed respiratory situations and the combinations of these demand attention. Whenever the condition can be anticipated, measures for prevention will prove more valuable than will measures for relief. Thus in the presence of chronic passive congestion, care with the diet, the proper use of digitalis, draining of embarrassing liquid from the pleural or peritoneal sacs and the judicious use of diuretics exhibited early may prevent serious complications.

In the distension of the bowel arising in pneumonia or typhoid fever, the toxic atony of the colon by reducing the pressure of the intestinal gases may be responsible for the rapid unloading into the colon of blood gases. Here measures to combat atony or to increase intra-abdominal pressure require consideration. These therapeutic problems are very clearly discussed by Alvarez.

Fifteen and more years ago when treating diabetic patients before the advent of insulin, physicians used diets containing much roughage in the form of five per cent. vegetables. Some patients returned blessing us for relieving their constipation for the first time in their lives. Others, apparently treated similarly, developed an initial constipation. Worried, nervous and sleepless patients and patients affected with arterial hypertension when temporarily placed on sedatives frequently experienced relief from constipation. Myxedematous patients had constipation relieved by thyroid extract. Patients with achlorhydria sometimes were relieved of costiveness by hydrochloric acid. Recently, we have seen some surprising results in gastrointestinal irregularities following the correction

of certain avitaminoses. All of us know of occurrences similar to these which at the time seemed unrelated to anything in particular or even contradictory of our teachings; too many of these occurrences have been dismissed from our minds as inexplicable, insignificant or incorrect. If we have been wise enough to record them we may have profitted later when we realized their significance. Now let us consider briefly certain of these matters concerned with constipation and let us determine if possible how the physiological facts which we have reviewed explain the occurrences and clarify the course of the treatment by which the constipation may be corrected or relieved.

#### (1) DEFECTION REFLEX

A very large portion of constipated persons are such, at least in part, because of lack of response to the urge for defecation. Sheer laziness, prudery, the demands of occupation, disgusting or ill suited toilet facilities are among the reasons why this situation is possible. When the "call" is not answered the sensitivity to the defecation stimulus tends to become weak and may disappear if constantly there is disregard of the natural sequences.

A very important sub-group is that in which there is irritation or inflammation of the ano-rectal region which renders defecation difficult or painful. Such conditions are fistula, fissure, ulceration, painful hemorrhoids, etc. Here, however, the element of sphincter-spasm enters accompanied by secondary factors which take such patients out of the class of those who merely ignore the normal defecation reflex. Furthermore, the local pathology may inhibit the complete development of the reflex. Hard, dehydrated, fragmented, fecal material may traumatize the anal region and establish sphincter-spasm.

Inflammation of nearby organs (prostate, uterus etc.,) similarly may cause constipation reflexly by holding the feces above the point where the defecation reflex is initiated.

Finally there is the group (tabes dorsalis) where the nervous mechanism itself is injured. This is especially serious when the sensory pathways are not functioning.

#### (2) DIETARY FACTORS

Sufficient tension must be developed in the rectum to set up the defecation reflex; insufficient food of itself may provide a deficient residue and no stimulation may occur. Infrequent eating may do the same and cause the reflex to occur at such widely separated times that the colon's function is weakened. The so-called "greedy colon" may absorb food and water so completely that not enough residue remains. Obstruction to the entrance of sufficient residue into the colon may occur when there is narrowing of the ileocecal valve or obstruction due to organic lesions or spasms located higher up, as in the esophagus, at the cardia or the pylorus. Pain and vomiting, of several origins, may inhibit the taking of food or cause its loss after ingestion and hence give rise to little residue in the colon. Deficient water intake may cause such a degree of inspissation of the feces that they become poorly effective stimulators of the defecation reflex or they cause local irritation which induces spasm and, secondarily, constipation. In diabetes, mellitus and

insipidus, in hyperthyroidism and in fevers so much ingested water is diverted from the bowel through the kidneys, skin or lungs that constipation may follow.

### (3) LAXATIVES, CATHARTICS AND PURGATIVES

Strictly speaking these have no separate place in the classification which this article follows but their wide use in constipation emphatically requires attention. By causing irritation and inflammation, by abstracting water and by reducing residue they cause spasm, alter secretions and reduce the fecal contents so much that no normal defecation reflex can arise. Thus they themselves may cause constipation. After the alimentary tract has been purged only harm can be done when more catharsis is sought within a period of 24 or even 48 hours. Time should be given for a sufficient residue to collect.

### (4) EXERCISE

The sedentary life leads to weak skeletal muscles. When the abdominal muscles are weak and of poor tone, and posture is incorrect, intra-abdominal pressure falls and this favors constipation. Weak muscles also render defecation difficult from lack of expelling power. Modern conveniences have not reduced the problems of constipation. The blessings and comforts of the modern toilet are outweighed by the ease of living which the elevator, washing machine, vacuum cleaner and automobile have brought to us. We have not learned to make up in pleasurable bodily exercise what we lost in unpleasant work. On the other hand muscular athletes often are constipated. Yet some persons with flabby muscles, sagging, protruberant abdomens and intestinal tracts in very low positions show no evidence of trouble. When change from activity to non-activity quickly is followed by constipation, as when one changes to a sedentary occupation or is forced by some circumstance to stay in bed, the significance of the inactivity seems clear. Departure from accustomed physical activity is a factor in constipation.

### (5) OBSTRUCTION

Bands and adhesions may kink and constrict portions of the colon. This constriction occurs most frequently in the region of the terminal ileum, the cecum, along the ascending colon and at the hepatic and splenic flexures. Right sided stasis is a well recognized result. Similar processes may occur at other points but are less common although a special and well appreciated kind of obstruction is due to malformations at the sharply-angled, pelvi-rectal junction.

Obstruction rarely arises from cicatricial lesions in the gut wall, such as healed tuberculous ulcers. Lymphogranuloma inguinale of the anus is an exception. Carcinoma commonly gives no striking evidence of its presence until there is nearly complete stenosis; this hardly comes within the scope of this paper.

### (6) STASIS

Many conditions are grouped under this head but all have the common effect of causing stagnation and delay of the fecal stream. When such occur, extraction of water rapidly takes place leaving hard fecal masses which irritate and add to the factors originally causing stasis.

Emotional states are fundamental causes of stasis. Irritating food residues, lead, tobacco, and caffeine, organic disease of the lumbar cord and irritated or inflamed mucous membrane however caused may be responsible for the condition.

### (7) SPASTIC CONSTIPATION

The old classification of constipation recognized "atonic" and "hypertonic" or "spastic" types. There is little or no supporting evidence for atonic constipation. In the spastic type, the peristaltic contractions are persistent and usually are brought on by some irritating factor such as those above mentioned. Great care in reaching a diagnosis must be used to establish the constancy of spasticity. Usually the spastic area is limited in extent. In his valuable book, "Functional Disorders of the Large Intestine", Buckstein outlines several types. He discusses "proctogenic" constipation due to spasm of the sigmoid, rectum and anal sphincters; ileal stasis due to cecal stasis and spasm of the ileocecal sphincter; colonic stasis, diffuse in distribution or localized to the cecum and ascending colon, sometimes other areas, with spasm of the distal colon; ceco-colic stasis with spasm about the hepatic flexure or any point from there onward to the splenic flexure; stasis in the transverse colon, fragmented feces beyond the splenic flexure and functional or organic obstruction at the splenic flexure accompanied by marked spasticity of the descending colon. Note in each instance that the stasis is proximal or cephalad to the point of spasm. This last type of stasis deserves comment in that there may be sharp angulation of the splenic flexure as a consequence of adhesions or gaseous distension, conditions which cause partial occlusion. This is accompanied by upward displacement of the diaphragm and the heart with resulting, annoying, cardiac oppression; rapid and small or an irregular pulse, with or without colic and acutely distressing gastro-intestinal crises. An "air lock" intensifies the situation. A similar situation may arise at the hepatic flexure.

A common form, namely stasis limited to the rectum and sigmoid has been named "dyschesia". Apparently it arises from neglected defecation reflex with loss of sensitivity, over distension of the rectum, impairment of the rectal musculature and reduction or loss of the power of expulsion. Large fecal masses accumulate, become inspissated, and cause catarrhal inflammation. This engorgement of the bowel aggravates the situation. The colonic contents actually may have to be dug out from below with a spoon or curette.

The increase in the tonus of the sphincter may be but part of the general tenseness of all of the voluntary muscles as exhibited by tired, highly nervous, psychically unstable persons.

### TREATMENT

The formation of a natural habit of bowel emptying most emphatically should begin in infancy. Just after breakfast, physiologically, is the ideal time for defecation. Perhaps we should say "after the meal which closes the longest fast period of the day". The attempt to expel a stool should be made then even though there is no "call". Voluntary action, as by forcible contraction of the abdominal muscles, may push the feces down into the rectum and thus start the reflex. "Calls" should be responded to at whatever time in the day they may come. Of great importance

as a prophylaxis against constipation is the rising of individuals at an hour sufficiently early and the opening of schools and offices at an hour sufficiently late that all persons may have opportunity to have stools after breakfast and before the day's work starts.

The diet should be fitted to the problem. For spasm in general, a smooth diet relatively free from roughage and cellulose should be exhibited. Remember that muscle spasm is only one factor in the constitutional make up of a high tension individual. Rest, relaxation, elimination or reduction of responsibilities, the development of a more leisurely spirit and sometimes, medicinally, the administration of sedatives are measures of importance.

If the patient is of the kind who responds to all digestive disturbances by the elimination from his diet of first one food and then another, the problem of lack of food volume, calories, vitamins and roughage may arise. My own experience has taught me that this occurs with considerably greater frequency than I at first supposed. Experience with severer grades of avitaminosis has taught me to recognize the milder forms of vitamin lack. Frequently, such patients resist the replacement in their diet of the vitamin-rich foods because of the distress they arouse. In such circumstances the concentrated preparations of vitamins are of a value which outweighs their great cost.

Thorough food mastication should be insisted upon. Diets high in carbohydrates, especially glucose, should be used guardedly where bowel distension complicates the constipation. Milk often causes similar trouble. In certain patients, when enteroptosis is associated with constipation, hyperalimentation may be called for but in these subjects where ptosis actually causes deficient food mixing and food stasis, periods of complete rest, physical and mental, and the application of abdominal supports, properly fitted with pads, while in the prone position, are valuable adjuncts to dietotherapy. When hyperchlorhydria is present a high fat diet tends to alleviate the condition. In stasis, especially when of the right colon, cellulose should be limited in the diet. Abundant water should be taken regularly unless there are specific, important contraindications.

Bran or bran-containing, so-called "health foods", should be used cautiously. Death has followed its use due to impaction and subsequent rupture of the intestine. These occurrences are not easily detected in the making, however in elderly people the terminal symptoms may appear acutely and create puzzling diagnostic problems.

In the hands of many atropine is believed useful in managing spastic constipation. It must be given in full physiological dose for the individual. The sedatives, bromide and chloral, frequently are considerable aids in securing bowel relaxation in the tense individual. Some clinicians believe that thyroid extract is valuable in treating the constipation of myxedema. The constipation occasionally noted with Grave's disease may become less pronounced after partial thyroidectomy.

Mineral oil or agar, separately or together, are of very real help in starting patients back toward normal functioning. Especially are they valuable when right colon stasis and inspissation of the feces are factors. The action of mineral oil in preventing the absorption of the fat soluble vitamins must be circumvented.

Enemata of plain tap water or physiological saline solution used simply to arouse the defecation reflex may help in the re-education of the bowel. They should not be used constantly or over long periods. Colon irrigations and enemata while of real value undoubtedly are abused to a serious degree; it is to be hoped that present conditions have awakened many patients to the fact that they are better off without long courses of these treatments unless the colon lavage is given under competent medical guidance.

Local anal and rectal irritation should be treated carefully. Often the aid of a proctologist is invaluable in relieving such lesions and shortening the period of illness. If low rectal and anal affections are present the feces should be kept soft and non-irritating. In selected minor rectal and sphincter lesions, I have found small enemata of tannic acid solution or a strong infusion of tea leaves great help particularly when such enemata are at a temperature of 100° F. and are instilled slowly with the patient lying on his back.

Irritating conditions of systemic or constitutional origin as causes of colon spasm should receive appropriate local or general treatment as indicated. At times surgery may be called for, but the variety of conditions demanding such cannot be discussed here.

Gymnastic and outdoor exercises, hydrotherapy and massage all have their places in treatment of certain patients. However it is very unlikely that any so-called "manipulations" will move fecal masses along the colon. Such was the abdominal massage of olden days carried out with the aid of a heavy iron ball.

Finally, when kinking, obstruction, diverticula, etc., are the causes of constipation, surgery may be of the greatest service. It should be decided upon only after very careful observations and carried out with great judgment and skill. Too many instances of constipation and obstruction have followed surgical operations. The surgery requisite for the correction of some of these conditions entails a very high degree of technical skill and judgment.

It must be evident from this review that constipation not only is an important subject in itself but that it is the presenting syndrome of a number of medical conditions which themselves must be attacked if success is to follow treatment. A few such conditions may be listed: drug addiction, pituitary conditions of several types, diabetes mellitus, obesity, malnutrition, achlorhydria, polyneuritis, scurvy, pellagra, gout, tuberculosis, pneumonia and other fevers, concussion of the brain, epidemic encephalitis, tabes dorsalis, arterial sclerosis and peptic ulcer. Successfully to deal with the constipation syndrome in many cases requires most carefully taken and searching histories, exhaustive physical examinations, and general laboratory, metabolic and roentgenologic studies. Constipation presents for its etiologic solution problems demanding the highest professional skill; in its treatment great ingenuity, patience and medical and nutritional experience are called for. In its surgical management all fields of operative procedure may have to be entered. In certain instances, advances in neuro-surgery offer much promise but until much more is known of the function of the spinal nerves and the ganglia restraint should be the rule in this field.

# The Weltmann Test in Diseases of the Liver\*\*

By

MANFRED KRAEMER, M.D.  
NEWARK, NEW JERSEY

THE difficulty in making a positive clinical differentiation between a parenchymatous (catarrhal or cirrhotic) and an obstructive jaundice is generally recognized. The many tests of liver function (1, 2, 3, 4, 5, 6) now in vogue suggest that likewise there is no absolute laboratory procedure which can tell us whether, in a given case of jaundice, we are dealing with a parenchymatous or an obstructive process.

Many authors (7, 8, 9) find the galactose tolerance test of Bauer most valuable in making a differentiation, but others, notably Banks, Sprague, and Snell (10) feel that its usefulness is very much limited. In private practice, and when performed promptly after the appearance of jaundice, our experience with Bauer's test has been favorable. However, in the wards of a public hospital the performance of the test is too time-consuming and expensive. Where chemicals are purchased by "bids," an impure galactose may be substituted for the more costly C.P. product. This use of impure galactose makes results very difficult to evaluate. The galactose test takes five hours for its completion and requires the collection of all urine passed within that time. In wards inadequately staffed, patients unwittingly void specimens into urinals which are emptied into a toilet instead of being saved. In patients with associated prostatic disease, diabetes, or kidney disfunction, it is almost impossible to get an accurate idea of galactose utilization.

The above is my *apologia* for the discussion of a test for liver disease which may prove as valuable as the galactose tolerance test but which is both simpler and easier to perform and which can be carried out at a negligible cost.

Oskar Weltmann, a clinician and physiological chemist, who had for some time been studying liver disease (11, 12, 13, 14, 15) published in February, 1930, (16) the result of some researches on the effect of certain pathological processes on the coagulability of the blood serum. By October, 1930, (17) he had applied these changes in blood serum coagulability to a test for the differential diagnosis between obstructive and parenchymatous states of the liver. He called his test the 'Serums Koagulations Band' and abbreviated this title to 'K.B.' This test was later elaborated upon by Weltmann (18). European writers have used the test not only in differentiating hepatic diseases but also as an aid to the diagnosis of a great variety of disease conditions. No reports have appeared in the English literature. In this paper, we shall confine ourselves to a description of the test, reports of the

literature, and a preliminary report of our findings with this test in hepatic diseases.

## DESCRIPTION OF THE TEST

If blood serum be diluted with distilled water and boiled, the coagulability of the serum depends upon the presence of a certain minimal quantity of electrolytes. Thus, the protein in a 1:50 dilution of blood serum in distilled water does not coagulate by boiling, but coagulation immediately appears if a small amount of sodium chloride, calcium chloride or barium chloride is added to the boiling dilution.

Weltmann determined that, in a boiling 1:50 dilution of normal blood serum, the lowest concentration of calcium chloride solution in which coagulation of the serum protein takes place is from .03 to .04 per cent. That is, if 0.1 c.c. of normal blood serum is added to 5 c.c. of .02% calcium chloride solution and boiled, no coagulation takes place. However, if 0.1 c.c. of normal blood serum is added to 5 c.c. of .04% calcium chloride solution and boiled, the serum protein coagulates.

It was found that inflammatory and exudative processes (pneumonia) changed the blood serum so that the protein was coagulated in only the more highly concentrated solutions of boiled calcium chloride, as .08%. On the other hand, disease of the parenchyma of the liver, cardiac decompensation with stasis, and fibrous forms of tuberculosis so changed the blood serum that the protein was coagulated in much lower dilutions of boiled calcium chloride, e.g. .02%. These observations have been confirmed by a number of investigators to whom I shall refer later.

On the basis of these findings the Weltmann serum coagulation test was devised. The technic follows:

## TECHNIC

In stock are kept eleven large (500 c.c.) bottles of the following solutions of anhydrous calcium chloride: 0.1%, .09%, .08%, .07%, .06%, .05%, .04%, .035%, .03%, .02%, .01%. These bottles are numbered from 1 to 11. Number 1 corresponds to 0.1% and number 11 to .01% dilution of calcium chloride.

Eleven test tubes are placed in a rack. To each tube 5 c.c. of a different one of the dilutions of calcium chloride is added. A different 5 c.c. volumetric pipette is used for each bottle. The tubes are numbered 1 to 11 to correspond to the stock bottles. Then to each test tube 0.1 c.c. of the serum to be tested is added, this serum having been collected by the usual method as for a Wasserman test. The tubes are shaken and then placed in a boiling water bath for fifteen minutes. A large water bath is used so that the entire test tube rack may be placed into the bath and removed without disturbing the position of the tubes. After fifteen minutes boiling, the tubes are removed from the water bath and the weakest solution of calcium chloride in

\*From the Medical Service of Dr. Frederick Alling, Newark City Hospital.  
Submitted December 3, 1934.



which coagulation has taken place is determined. In the reading, lumping of the protein not turbidity is considered. The number of the tube containing the weakest solution in which lumping (coagulation) takes place determines the length of the coagulation band (C.B.).

In normal serum, the coagulation band has almost a constant length reaching to the 7th or 8th tube, corresponding to a calcium chloride dilution of .04 to .035%. In certain diseases the coagulation is either shortened (coagulation in less than 7 tubes) or lengthened (coagulation in more than 8 tubes). A short C.B. or no coagulation at all is observed in pneumonia, acute rheumatic fever, and in other infectious or exudative processes. A lengthened coagulation band occurs in cirrhosis of the liver, in all parenchymatous affections of the liver, and in all fibrous processes.

The method has its limitations in the cases in which exudative-inflammatory and fibrous processes are associated. In these cases a normal C.B. may result from the antagonistic effect of the two processes. Thus extensive destruction of liver tissue by fibrosis following obstructions by a neoplasm may lead to a lengthening of the band. (cf. Table, Case 24)

#### REVIEW OF LITERATURE

As previously mentioned, the test has been found useful in the diagnosis and prognosis of several diseases. The value of the test in the differentiation of exudative and fibrous tuberculosis was first shown by Weltmann (16, 17) and has been confirmed by others. (19, 20, 21, 22, 23) Rohacova and Weicherz (21) and others (19, 22) found the C.B. of greater prognostic value in tuberculosis than the sedimentation rate of erythrocytes. Writers who have employed the test have found it of diagnostic and prognostic value in pleurisy (24), gynecological conditions (25, 26), and pneumonia (18). Klaston (27) has described changes in the C.B. in pregnancy associated with such complications as pyelitis and mastitis or alterations in the liver. Kretz (28) studied the C.B. of 420 patients before and after various abdominal operations and noted a shortening of the band post-operatively with a return to normal quite rapidly. Such complications of the recuperative processes as abscesses, and thrombophlebitis caused continued shortening of the band.

The value of the coagulation band in the differential diagnosis of liver diseases has been established by many writers (16, 17, 18, 29, 30, 19, 31, 32, 33).

We have made no study as to the reasons for the phenomena observed in this test. Some function of the liver must be responsible for the changes found, because in other diseases in which hepatic function may be involved, as in pernicious anemia (cf. Table, Cases 19, 20 and 21), diabetes melitus, and chronic alcoholism the effect is the same as that observed in cirrhosis (33). Weltmann (18) and others (34) showed the reaction depends upon a change in the serum albumen, and not in a change in the serum calcium as suggested by Kaiser (20). Although the cause of the coagulation band is unsolved, its regular and constant changes in certain diseases and its simple technic may make it a useful diagnostic means, especially in the field of liver pathology.

#### COMMENT

Our results, which are shown in the accompanying table, have in the main agreed with those of the

TABLE I  
*The Coagulation Band (C.B.) In 25 Cases of Liver Disease.*

| Case | Age | Sex | Ict. Index | C.B. | Diagnosis                                                                           |
|------|-----|-----|------------|------|-------------------------------------------------------------------------------------|
| 1.   | 51  | F.  | 22.5       | 8    | Stone in comon duct. (Laparotomy)                                                   |
| 2.   | 46  | M.  | 10         | 8    | Prostatic cancer metastasizing to liver and obstructing bile ducts. (Autopsy)       |
| 3.   | 59  | M.  | 33         | 7    | Cancer of pancreas. (Laparotomy)                                                    |
| 4.   | 75  | M.  | 10         | 9    | Cirrhosis of liver.                                                                 |
| 5.   | 50  | F.  | 100        | 11   | Parenchymatous jaundice and cirrhosis.                                              |
| 6.   | 40  | M.  | 18         | 10   | Cirrhosis of liver.                                                                 |
| 7.   | 50  | M.  | 10         | 11   | Cirrhosis of liver. (Esophageal varices)                                            |
| 8.   | 47  | M.  | 10         | 10   | Cirrhosis of liver.                                                                 |
| 9.   | 72  | M.  | 29         | 10   | Cirrhosis of liver. Pancreatic cancer with extensive metastasis to liver. (Autopsy) |
| 10.  | 33  | F.  | 30         | 11   | Congenital hemolytic icterus. (Splenectomy)                                         |
| 11.  | 45  | M.  | 100        | 10   | Arsphenamine hepatitis. (Autopsy)                                                   |
| 12.  | 26  | M.  | 80         | 10   | Parenchymatous jaundice.                                                            |
| 13.  | 59  | F.  | 150        | 10   | Parenchymatous jaundice.                                                            |
| 14.  | 57  | F.  | 30         | 10   | Parenchymatous jaundice.                                                            |
| 15.  | 66  | M.  | 30         | 10   | Parenchymatous jaundice.                                                            |
| 16.  | 63  | F.  | 15         | 10   | Cholangitis. (Laparotomy)                                                           |
| 17.  | 52  | F.  | 31         | 10   | Cholangitis. (Laparotomy)                                                           |
| 18.  | 39  | M.  |            | 11   | Cholangitis. Cholecystitis. (Laparotomy)                                            |
| 19.  | 30  | M.  | 15         | 10   | Pernicious anemia.                                                                  |
| 20.  | 30  | M.  |            | 10   | Pernicious anemia.                                                                  |
| 21.  | 53  | M.  |            | 10   | Pernicious anemia.                                                                  |
| 22.  | 52  | M.  | 48         | 9    | Primary cancer of bile ducts. (Laparotomy)                                          |
| 23.  | 36  | M.  | 15         | 9    | Miliary tuberculosis.                                                               |
| 24.  | 58  | M.  | 75         | 10   | Cancer of head of pancreas, with obstruction of common duct of long duration.       |
| 25.  | 47  | M.  | 50         | 10   | Primary cancer of liver. (Laparotomy)                                               |

writers to whom we have referred. The test should prove valuable chiefly in determining whether or not a given case of jaundice is of an obstructive or of a parenchymatous nature. The cases of pernicious anemia and the case of familial hemolytic icterus showed results similar to those in parenchymatous jaundice, i.e. lengthening. The test does not aid in differentiating between an obstructive jaundice due to stone (Case 1) and one due to neoplasm. Case 3). In both the C.B. would be normal. In either case, however, surgical exploration is generally considered the proper procedure. Uniformly the patients with simple parenchymatous icterus (catarrhal jaundice) and those with cirrhosis with icterus showed lengthening of the band. Unfortunately, the number of cases of early obstructive jaundice coming to our attention have been few—only three cases in the past year. Case 24, which was diagnosed as carcinoma of the head of the pancreas showed lengthening. The obstruction, if this diagnosis was correct, (and we are not sure that it was, since the patient improved and left the hospital without a laparotomy) was of long standing and probably resulted in back-pressure on the liver with considerable parenchymatous damage, (as occurred in Case 9) which would have accounted for the lengthening of the band.

Our material has been too limited to enable us to evaluate this test properly. We present this preliminary report in the hope that the use of this test will be investigated by others. We believe that further use and study of the test in a large number of cases by critical investigators may elucidate a number of clinical problems.

#### ACKNOWLEDGMENT

I wish to acknowledge the assistance rendered by Dr. George Hewson.

## REFERENCES

1. Strauss, H.: Zur Funktionsprüfung der Leber, *Deutsche med. Wchnschr.* 27: 757, 1901.
2. Bauer, Richard: Über die Assimilation von Galaktose und Milchzucker beim Gesunden und Kranken, *Wien. med. Wchnschr.* 56: 20, 1906.
3. van den Bergh, A.A.H.: *Presse med.* 29:441, June 4, 1921. The Dinzo Test for Bilirubin in Blood.
4. Rosenthal, N. and White, E. C.: Clinical Application of Bromsulphalein Test for Hepatic Function, *J.A.M.A.* 84:112, April 11, 1925.
5. Wallace, G. H., and Dimond, J. S.: The Significance of Urobilinogen in the Urine as a Test of Liver Function, *Arch. Int. Med.* 35:628, June, 1925.
6. Lichtman, S. S.: Cinchopen Oxidation Test of the Function of the Hepatic Cells, *Arch. of Int. Med.* 48:95, July, 1931.
7. Shay, Harry and Schloss, Eugene: Painless Jaundice: Its Differential Diagnosis by Galactose Tolerance Test, *J.A.M.A.* 98:1433, April 23, 1932.
8. Robertson, W. E., Swalm, W. A., and Kunkelmann, F. W.: Functional Capacity of the Liver, *J. A. M. A.* 99:2071, Dec. 17, 1932.
9. Rosenberg, D. H.: The Galactose and Urobilinogen Tests in the Differential Diagnosis of Obstructive and Intrahepatic Jaundice, *Ann. Int. Med.* 8:60, July, 1934.
10. Hanks, B. M., Sprague, P. H., and Snell, A. M.: Clinical Evaluation of the Galactose Tolerance Test, *J. A. M. A.* 100:25, 1897, June 24, 1933.
11. Weltmann, O., and Neumayer, K.: Das Fibrinogen in diagnostischen Klinik der Leberkrankheiten, *Med. Klin.* 21:629, April 24, 1925.
12. Klimesch, E., and Weltmann, O.: The Clinical Value of the Determination of Fibrinogen, *Med. Klin.* 23:146, July 29, 1927.
13. Weltmann, O., and Jost, F.: Über die Adsorption des Bilirubins an das Eiweiß, ihre Bestimmung und klinische Verwertung, *Deutsches Arch. f. Klin. Med.* 161:203, 1928.
14. Weltmann, Oskar: Die Differentialdiagnose des Ikterus, *Praktische Arzt.* 13:216-243, May und June, 1928.
15. Weltmann, Oskar: The 'Cirrhosis of the Liver, *Wien. klin. Wchnschr.* 41:1301-1349, Sept. 13, 20, 1928.
16. Weltmann, Oskar: Über die Spiegelung exsudativ-entzündlicher und fibroser Vorgänge im Blutserum, *Med. Klin.* 26:240, 1930.
17. Weltmann, Oskar: Pathology of the Liver, *Wien. klin. Wchnschr.* 43:1301, Oct. 23, 1930.
18. Weltmann, Oskar and Medvei, C. V.: Investigations on Serum Coagulation, *Ztschr. f. klin. Med.* 118:670, 1931.
19. Schneiderbauer, A.: The Coagulation Band and its Position in the Clinic, *Wien. klin. Wchnschr.* 46:385, March 31, 1933.
20. Kaiser, T.: Beitrag zur Weltmannschen Serumkoagulation bei Lungentuberkulose, *Beiträge z. Klin. d. Tuberk.* 83:271, May, 1933.
21. Rohacova, D., and Weichherz, E.: Das Koagulationsband von Weltmann bei Tuberkulose, *Med. Klin.* 29:1410, Oct. 13, 1933.
22. Makitra, A., and Tyndel, M.: Practical Value of Weltmann's Coagulation Band for Diagnosis and Prognosis of Tuberculosis, *Beiträge z. Klin. d. Tuberkulose*, 84:265, Feb. 22, 1934.
23. Dissmann, E.: Value of Weltmann's Reaction in Estimation of Pulmonary Tuberculosis, *Beiträge z. Klin. d. Tuberk.* 84:270, Feb. 22, 1934.
24. D'Alessandro, R.: Weltmann Coagulation Test in Pleurisy, *Il Policlinico*, 41:623, April 9, 1934.
25. Klasten, E.: Die Verwertbarkeit und Entwicklung des Koagulationsbandes, *Zentralbl. f. Gynak.* 56:939, 1932.
26. Purper, F. G.: Weltmann's Coagulation Band in Inflammations of Adnexa, *Monatsschr. f. Geburtshilfe u. Gynak.* 97:138, June, 1934.
27. Klasten, E.: Die Verwertbarkeit des Koagulationsbandes in der Geburtshilfe und Gynäkologie, *Med. Klin.* 28:258, Feb. 19, 1932.
28. Kretz, J.: Das Verhalten des Weltmannschen Koagulationsbandes nach operativen Eingriffen, *Wien. klin. Wchnschr.* 46:492, April 21, 1933.
29. Trost-Scherlechner, Paula: Beiträge zur Serumkoagulation nach Weltmann, *Wien. med. Wchnschr.* 82:1276, Oct. 1, 1932.
30. Skouge, Erling: Der Wert der Takata-Ara-Reaktion und der Koagulationsbestimmung bei Leberkrankheiten, *Klin. Wchnschr.* 12:265, 1933.
31. Weltmann, O., and Sieder, R.: Significance of Weltmann's Coagulation Band for Diagnosis of Hepatic Diseases, *Wien. Archiv f. innere Med.* 24:321, Feb. 10, 1934.
32. Massobrio, E., and de Micheli, U.: Serum Coagulation of Weltmann in Hepatopathy in Relation to Protein Picture of Serum, *Minerva Medica*, 1:147, Feb. 3, 1934.
33. Pellegrini, M., and Barsini, G.: Behavior and Significance of Weltmann's Serum Reaction in Some Diseases: Research on Behavior of Electrolyte Threshold of Coaguloflocculation to Heat of Exudates, Transudates, and of Normal and Pathologic Cerebrospinal Fluid, *Minerva Medica*, 1:154, Feb. 3, 1934.
34. Medvei, C. V., and Puschke, K. E.: Die Beeinflussung der Takata-Ara-Reaktion und des Koagulationsbandes durch Heparin, *Klin. Wchnschr.* 12:1910, Dec. 9, 1933.

## A B S T R A C T S

G. M. DACK AND ELIZABETH PETRAN, Chicago, Ill.

*Experimental Dysentery. Pages 1-6, 1934, Vol. 55, No. 1.*

A study was made of bacterial activity in two isolated segments of large intestine of monkeys into which dysentery bacilli were injected. This gave opportunity to determine bacterial changes in the absence of micro-organisms carried by the fecal stream. The opportunity for these dysentery bacilli to establish themselves may be quite variable. Freshly isolated virulent strains of these organisms, inoculated into isolated loops of colon in adult monkeys, produced an infection in the loops, which resulted in a profuse bloody mucous discharge. Marked systemic reaction accompanied the infection in the loops of intestine; this was characterized by pallor, loss of appetite, leukopenia, loss of weight, and prostration. The acute symptoms appeared within forty-eight hours and lasted three to four days. Within a week the discharge from the fistulas had ceased and systemic symptoms had disappeared. The severe systemic reactions may have been the result of absorption of toxins. Agglutinins for *Bacterium dysenteriae* (Flexner) were demonstrated in the serum of the animals. No evidence of infection was apparent in that portion of the colon through which the fecal stream passed.

However, severe symptoms of dysentery developed in two large adult monkeys which were fed the same strains of organisms.

It would seem, then that the fecal strain is not essential for the dysentery bacillus to establish itself and produce infection.

J. Arnold Bargaen, Rochester, Minn.

SCHIFF, LEON, AND SENIOR, FANNY A.

*Jaundice, With Particular Reference to Galactose Tolerance, Jour. of the A. M. A., 105:1924, Dec. 22, 1934.*

The authors studied 100 cases of jaundice with particular reference to galactose tolerance.

There were 50 cases of catarrhal jaundice. In forty-seven of these cases a positive galactose test (excretion of three grams or more) was obtained on the first examination. In two additional cases positive tests were obtained on second examination.

In fifteen cases of toxic hepatitis the test was positive in fourteen.

In a group of twenty cases of obstructive jaundice due to stone in common duct, cholangitis, pancreatitis, pancreatic carcinoma, and pancreatic cyst, the galactose test was negative in all of these cases.

In ten cases of cirrhosis of the liver the galactose test was negative in six cases and positive in four.

In carcinoma of the liver, the galactose test was negative in four out of five cases.

In the above study serum bilirubin determination and bromsulphalein retention tests were made. From comparison of these studies the authors find that the galactose tolerance bears no relationship to the degree or duration of the jaundice or to the amount of bromsulphalein retention.

Discussions by Dr. Harry Shay and Dr. F. C. Mann follow.

Francis D. Murphy, M.D., Milwaukee, Wis.

# Diverticula of the Duodenum and Diabetes

By

WILLIAM B. THORNING, Jr., M.D.

and

HOWARD F. ROOT, M.D.

BOSTON, MASSACHUSETTS

THE occurrence of five duodenal diverticula in a diabetic patient, previously operated upon for gall stones, raises numerous questions regarding the etiology of diverticula, their differential diagnosis, and treatment. Although often regarded as causing no symptoms, recent reports indicate that such diverticula may simulate duodenal or gastric ulcer, gall bladder or pancreatic disease. Indeed acute and chronic pancreatitis have been attributed to extension of inflammation from such diverticula. The association of duodenal diverticula and diabetes, therefore, has a special interest. The following cases illustrating the complexities arising are presented with a brief discussion of diverticulosis of the duodenum and ileum.

## HISTORY

Case I (3782), Jewish housewife, aged 66 years entered the New England Deaconess Hospital October 25, 1934, complaining of pyrosis, substernal pain and pain in either hypochondriac area coming on usually one hour after eating but frequently at night and often with nausea. Vomiting rarely occurs and she has had no hematemesis. Constipation, weakness, swelling of the upper abdomen and a loss of 22 pounds in weight during the last 5 years are recorded. Relief has been obtained frequently by induced vomiting and the use of alkalies but not by means of food.

The onset of these abdominal symptoms, although stated by the patient to have occurred about the time when she developed diabetes, December, 1923, is difficult to determine, owing to their possible confusion with symptoms related to her gall-stones. Previous hospital records show complaints of pyrosis and upper abdominal symptoms for 32 years.

Through the courtesy of Dr. George H. Stone of the Memorial Hospital, Worcester, Mass., her record from December 24, 1914, to March 13, 1918, is available and describes attacks occurring at irregular periods of chills, vomiting and marked pain in the left upper abdominal quadrant. These attacks began in 1902. At operation performed in 1915 at the Memorial Hospital, the following notes were made: "Right rectus incision, gall bladder exposed and found to be greatly thickened and adherent to surrounding structures. Gall bladder partially freed from adhesions and more fully exposed. Trocar and canula were inserted but no bile secured. Gall bladder opened and small amount of bile was drained out. Many soft stones were found and removed with curette. Common duct palpated and found to contain a mass of soft stones. Gall bladder completely freed from surrounding structures and amputated near base of cystic duct. A large amount of debris containing many small soft stones was curetted from common duct. A rubber tube was inserted in duct and two Penrose drains threaded with iodoform gauze placed in wound."

In 1918 she still complained of gas, vomiting and had had chilly sensations and fever.

Tuberculosis was suspected but no confirmatory evidence obtained.

Palpitation of the heart, dyspnea on exertion without edema of ankles and a ringing sound in left side of head were the only symptoms outside the gastro-intestinal tract at the present admission.

## PHYSICAL EXAMINATION

Weight 101 pounds (net), Blood Pressure 180/90.

A visible dilatation of the right carotid artery at the base of the neck one and one-half centimeters in length and breadth. Few subcrepitan rales at lung bases without dulness. The heart sounds were regular and of good quality with a systolic basal murmur which is accentuated over the aorta with the patient sitting upright. The heart was moderately enlarged, the total diameter by x-ray being 14.3 c.m., as compared with chest diameter of 23.9 c.m. and a calcified plaque was visible in the arch of the aorta. Radial arteries were tortuous and moderately sclerotic. The abdomen was mildly distended, not resistant but rather doughy without tenderness. Liver palpable two centimeters below costal margin but smooth. Extremities thin, musculature flabby, no edema, reflexes present and equal.

## LABORATORY DATA

The blood sugar values were 0.19 per cent fasting and 0.24 per cent after a meal, non-protein nitrogen 25 milligrams per 100 c.c. The first urine specimen contained 0.9 per cent sugar but thereafter was sugar free with doses of insulin ranging from 5 to 8 units. White blood count 13,700, hemoglobin 77 per cent (Sheftel) red blood count 4,800,000, differential count normal. Gastric aspiration with alcohol meal showed no free hydrochloric acid and strongly positive benzidine tests in five specimens. A little fresh blood was probably due to trauma from the tube. Electrocardiogram showed left ventricular preponderance. The S-T interval was depressed in Lead I and elevated in Lead III. The P-R interval was 0.14 seconds.

10/30/34 *Roentgen Examination of the Gastro Intestinal Tract*: The kidney outlines are obscured by fecal matter. The stomach is normal in size and position, and regular in outline. The duodenal cap is enormously dilated. Five diverticula are seen in the region of the duodenum varying in size from one and one-half c.m. to six c.m. in diameter. A diverticulum three c.m. in diameter is seen in the jejunum. The diverticula remained filled for a seven hour period. At this time the stomach is empty and the head of the column is in the rectum. In twenty-four hours there was a small quantity of barium in one of the diverticula. The barium is massed in the large intestine from the splenic flexure to the rectum. The remainder of the large intestine is empty. Diverticula of the duodenum, single diverticulum of the jejunum with delay and dilatation of the duodenal cap and hyperactivity of the colon. (Dr. I. K. Bogan) D.

In Figures 1 and 2 are shown the diverticula.

The patient became more comfortable while in bed, but pain in the epigastrium, gas and nausea have continued at home. On Dec. 18, 1934, she had gained 5 lbs. and had improved in general condition.



Case II (13253), physician, age 74 years, entered the New England Deaconess Hospital November 30, 1934. Diabetes began in June, 1934, with nocturia and later polydipsia and polyuria. The blood sugar was 0.40 per cent October 1, 1934.

His digestive symptoms first began in 1926. At this time the gall bladder and many stones were removed. He was fairly well until October, 1934, when jaundice appeared with loose clay-colored stools.

Upon admission his weight was 136 pounds, a loss of 20 pounds from his maximum weight. Jaundice was marked. A large hard nodular mass, apparently the liver filled the epigastrium. Ascites was present. The blood bilirubin was 7.5 milligrams and the blood sugar 0.19 (190 milligrams) per cent. He had taken 18 units of insulin daily.

The gastro-intestinal x-ray report follows: 11/30/34 Barium passed to the stomach without delay. Stomach normal in outline. Pylorus opened filling normal duodenal cap. The second portion of the loop emptied rather rapidly and there was a diverticulum within the loop. Examination fails to demonstrate any evidence of intrinsic disease of the esophagus, stomach or duodenum. The loop shows a diverticulum and adjacent portions of the loop empty rather rapidly. The loop is not increased in size. (Dr. Jack Spencer).

The diverticulum measured one and one-half inches in diameter and arose on the mesial surface of the descending portion of the duodenum apparently resting on the head of the duodenum.

Owing to his general condition, the apparently rapid growth of a carcinoma arising either in the pancreas or gall ducts, operation was not advised.

### DISCUSSION

The downward course of Case I over a period of five years may be attributed to several causes, cardiovascular disease, a possible gall stone in the common duct, a neoplasm and the results of the duodenal diverticula. In Case II we have no suggestion that the diverticulum is responsible for symptoms or pancreatitis. In attempting to evaluate the significance of the diverticula, their frequency without serious symptoms as well as the complications produced by them, must be borne in mind.

### INCIDENCE OF DIVERTICULOSIS

Autopsy figures indicate according to Fraser (1) that from 0.5 to 1 per cent of all individuals possess diverticula of the small intestine not including Meckel's type. The duodenum, jejunum and ileum are in the order named the most common locations. Fraser (1) also reports that of five thousand cases from one hospital only two cases of this condition were so diagnosed clinically. This discrepancy between autopsy and clinical reports is explained by the large percentage of cases which are symptom free or have mild unexplained symptoms. The incidence of diagnosis, however, is on the increase as Edwards (2) finds that by roentgenography the percentage of cases rose from 0.2 in the years 1925, 1926 and 1927 to 0.9 in 1928. At the latter date the technique of examination was changed to include roentgenograms made from various angles of exposure. Since that time the increase has maintained itself through 1931 in a total of 4,631 cases. Carlson (3) found 112 cases in the literature up to 1912 and up to 1933 found 423 of which 66 were diagnosed at operation. Their occurrence in diabetics must be rare.

Children rarely are found with the condition. Horton and Mucller (4) in 122 autopsied cases reported a

22 year old woman with diverticula as the youngest. Those found in children are usually thought to be enterogenous in origin. Her cases showed a marked preponderance in the male sex. Edwards (2) states the age incidence of formation is 35 to 40 years. In our Case I the diverticula were not discovered at operation performed in 1915, or noted in gastro-intestinal x-ray examination carried out in another hospital in 1932. If they were actually absent at those times, their formation has occurred at about the age of 65 years. The facts that they did not always fill with barium and that, in the presence of adhesions they may easily be missed at operation, together with the constancy of her symptoms for at least 32 years lead us to believe that they probably developed between the 30th and 35th year.

### CLASSIFICATION

Fraser (1) classifies diverticula of the small intestine under four headings. 1. The multiple false or acquired variety. 2. The enterogenous which are formed from islands of cells separated from the primitive gut, becoming hollow and attached to the intestine in later life. 3. The anomalous which include diverticula incidental to the drag of a tumor, adhesions often related to cholelithiasis and cholecystitis, a healing peptic ulcer with shortening the duodenum, the softening of glands, or a tumor in the intestinal wall. 4. Meckel's diverticulum. Chapman (5) introduces a separate class by excluding all cases that are not multiple.

### ETIOLOGY

The etiology of the condition has been reduced to three prominent factors by Fraser. (1) 1. Presence of greater pressure in the lumen of the intestine than is normal. One such cause is illustrated by a stricture distal to the diverticula with accompanying symptoms of long-standing rectal or vesicle tenesmus. 2. The position of the nutrient vessels. Nearly all diverticula unless very large can be shown to be adjacent to the blood vessels at their point of entry into the intestine. The blood vessels are two in number for each section of the intestine and Edwards (2) finds that when small, most diverticula are double, and with increase in size form one by fusion. Many large diverticula have a reminder of this in a dimpling of the fundus produced by the band of muscle which at first separated two sacs. In our case diverticula 1 and 2 may actually be such a single dumb-bell shaped diverticulum. Horton (4) does not find this relation to blood vessels is true in the duodenum but considers that bits of pancreatic tissue are very common in the longitudinal muscular coat serving as points of lowered resistance in the intestinal wall. 3. Defects in the longitudinal layer of muscle of the small intestine particularly along the mesenteric border. Through these defects is herniated the mucosa producing the diverticulum. This herniation takes place along the course of the artery which in itself forms a weakness in the circular muscle coat. These diverticulations are more prevalent in the proximal portions of the small intestine as the diameter in that area is three times that of the distal portion so that a constant amount of muscle has a greater area of distribution. This is consistent with the finding of more diverticula in the proximal portions. Butler (6) on the basis of experimental work postulates traction by unelastic arteri-



Fig. 1. Film taken 15 minutes after barium sulphate given by mouth. The course of the duodenum is marked by arrows. Diverticula 1, 2, 3 and 4 arise in the first portion of the duodenum, apparently from the upper and lower borders. Numbers 1 and 2 may in reality be a single dumb-bell-shaped diverticulum, but appeared to be two diverticula in close apposition. The extraordinary width of the first portion of the duodenum was unexplained. Diverticulum number 5 arises from mesial border of the descending portion of the duodenum, and projecting inward, apparently, together with number 2, is in close relationship with the head of the pancreas. The extraordinary redundancy of the duodenal cap is unexplained. Exposures made with patient lying down.

osclerotic vessels in addition to increased internal pressure as a factor and that the early herniations are of all four coats rather than of the mucosa alone.

#### FUNCTIONAL PATHOLOGY

When the small diverticula begin they are protruding into the mesentery between its peritoneal leaves and on enlarging tend to extrude themselves carrying a covering of peritoneum from the leaf of the mesentery with them. As the evaginations reach golf ball size or larger their own weight tends to cause sagging thus kinking the neck of the sac. This occlusion accounts for the gas formation and abdominal distention which are so common. Many duodenal diverticula, however, tend to burrow in relation to the pancreas and receive no peritoneal coat. Histologically, usually only mucosa, often atrophic, and areolar tissue with or without peritoneum are seen on the well developed diverticula; there being no muscle tissue there is no power to produce colic or to empty the sac contents although it is usually liquid chyme. However, in a diverticulum of the duodenum recently removed at operation at the Deaconess Hospital, a normal muscular layer was present. The response to gravity in the position assumed by the diverticulum explains the comfort obtained from lying down. Although the duodenum is the commonest site they are usually single here; the jejunum and ileum are less frequently the site, but when so usually bear multiple sacs, sometimes into the hundreds. The symptoms vary with the location, size and number and secondary complications. Fulde (7) has demonstrated the relationship of duodenal diverticula and chronic pancreatitis. He studied 207 cases of diverticulosis of the duodenum and in 28 cases found more or less significant accompanying diseases of the pancreas. Two cases showed adhesions due to peri-diverticulitis and peri-pancreatitis. In 8 cases there were more or less out-spoken chronic pancreatitis, 5 cases went to pancreatic necrosis, 3 cases of phlegmon of duodenum. Three cases of carcinoma of the pancreas accompanied duodenal diverticulosis. Diverticula are often, according to Fulde, the starting point of chronic processes in the pancreas, owing to their frequent position in the descending duodenum

on the side adjacent to the pancreas. The reason is the opportunity for stasis and bacterial decomposition of the duodenal contents in the pouches and sometimes the inflammatory processes in the neck of the diverticulum. Two things may happen: 1. Direct extension, by way of lymph channels, of the inflammatory process. 2. Indirectly by the contents of the sac passing through Vater's papilla into gall ducts or pancreatic ducts. Catarrh of the duodenum may be so produced. Repetition of these processes may cause chronic pancreatitis. Through swelling of the papilla Wirsung's duct may be closed and an atrophy of the pancreas follow. He reports three cases showing disturbances in the external secretory function of the pancreas with fat in the stools, absence of trypsin and lipase in the duodenal contents. However, none of these cases had diabetes. Kellogg (14) in his monograph on the duodenum does not mention diabetes in connection with duodenal diverticula.

#### DIAGNOSIS

Diverticulosis of the small intestine can occur without symptoms sufficiently definite to permit definite diagnosis. Fraser (1) goes so far as to say that three-fourths of the cases have no symptoms. However, in cases with multiple diverticula of the duodenum such as are here described, gastro-intestinal symptoms may well be attributed to this cause. The cases so far reported may be classified in several groups.

In one class an acute abdominal condition is presented perhaps with little or no history of previous discomfort. Cases clinically resembling perforated peptic ulcer, Flynn (8), intestinal obstruction, (6) general peritonitis, (1) and perforated gastric malignancy, Davis (9) have been described. In a third class a variety of complaints of long duration occur. In a series of 14 cases, Gibbon (10) found 10 which had a previous diagnosis of neurosis. Although there are no pathognomonic symptoms, three stand out as most frequent. 1. Marked rumbling of gas in the abdomen; 2. A soft upper abdominal distention noticed by the patient, and 3. Relief from gas and pain on lying down. In addition, periodic upper abdominal pain after meals, not usually relieved by food but alleviated by alkalies in addition to eructation, pyrosis, and borborygmus sometimes more annoying than the pain are described. Vomiting is variable, often produced voluntarily. Hematemesis and melena are rare. Constipation is most common and a definite weight loss hardly less so. Diagnosis must rest on the demonstration of diverticula by barium meal, possibly by the presence of air sacs in a flat abdominal plate. However, it is stressed by Edwards (2) that retention of barium for only an hour or two is not an adequate ex-

Fig. 2. Film taken 2 hours after barium by mouth. Diverticula 1, 2, 3 and 5 are clearly outlined but 4 is not seen.

planation for symptoms. Davis (9) presents a case with six-hour retention in a duodenal diverticulum but after removing a common duct stone the patient was relieved and continued to be so at a five year examination. In our case removal of gall-bladder and stones in the common duct gave no relief of symptoms. On the other hand, King (11) removed a duodenal diverticulum which emptied in six hours with relief, but was not followed. Many cases exhibit retention for twenty-four hours or more. Diagnosis at operation is not always easy. Fulde (7) explains the failure to find diverticula at operation as due to adhesions from peri-pancreatitis.

### DIFFERENTIAL DIAGNOSIS

The existence of diverticula having been demonstrated by roentgenogram, the practical problem becomes one of determining whether sufficient explanation of symptoms has been found, or whether other lesions are present.

The three conditions to be eliminated most commonly are ulcer of the stomach or duodenum by its absence in roentgenograms, gastric carcinoma by the same means, cholecystitis and cholelithiasis by appropriate studies. Repeated examination both by fluoroscopy and numerous plates taken from different angles may be necessary for their demonstration. Chronic pancreatitis, intestinal polyposis, and heart disease will occasionally have to be ruled out. Horton and Mueller's (4) studies indicate that 32 per cent of cases are associated with cholecystitis, the age incidence of the two being similar. It must not be thought that a stone in the common duct is ruled out by the absence of jaundice. Most observers agree that unless 6-hour retention of barium in the diverticula can be demonstrated, symptoms may not be attributed to this cause. The long duration of epigastric distress, pain, pyrosis, induced vomiting without hematemesis, absence of relief by food, but relief by change of position, characterize diverticula.

### TREATMENT

It seems reasonable to permit those cases of multiple small diverticula, without symptoms causing grave discomfort discovered accidentally by barium meal, to avoid operation. A low residue diet, avoidance of constipation and straining and removal of any known causes for intestinal delay are indicated. Those cases discovered at operation will be treated as their size, number and location indicate in the operator's judgment. Fraser (1) mentions two cases which were thought



inoperable when discovered at operation but subsequently had to undergo enterectomy in a second operation.

The group which present symptoms definitely related to the diverticula even if mild had best be operated upon, in Fraser's (1) opinion, as a spontaneous cure is impossible and practically all patients who later develop serious complications such as diverticulitis, perforation or intestinal obstruction, Abell (12) had had symptoms for a considerable period.

Barnes (13) gives the operative procedures applicable to the different situations arising as resection of the diverticula with suture, resection with inversion of the stump, inversion with or without resection, resection and suture with or without gastroenterostomy, gastroenterostomy with or without occlusion of pylorus, resection of bowel. These are serious operations, and not to be advised without careful consideration. As in our Case I, complications may be important, and the difficulty of assigning with certainty the symptoms in question to the diverticula is great.

### SUMMARY

Diverticula in the duodenum are reported in two diabetics with previous operation for gall-stones. The possibility that inflammation in or about such diverticula can by extension cause chronic pancreatitis and diabetes is not demonstrable in these cases. The persistence of digestive symptoms after a gall-stone operation may occasionally be due to such diverticula.

### REFERENCES

1. Fraser: *Brit. J. Surg.*, 21:183, 1933.
2. Edwards: *Clinical Journal*, 63:231, 1934.
3. Edwards: *Lancet*, 1:169, 1934.
4. Carlson: *Texas State J. M.*, 29:299, 1933.
5. Horton and Mueller: *Arch. Surg.*, 26:1010, 1933.
6. Chapman: *Ann. Int. Med.*, 7:1376, 1934.
7. Butler: *Brit. J. Surg.*, 21:329, 1933.
8. Fulde: *D. Arch. f. Klin. Med.*, 173:404, 1932.
9. Flynn: *Australian and New Zealand J. S.*, 3:192, 1933.
10. Davis: *Cal. and Western Med.*, 39:229, 1933.
11. Gibbon: *Radiology*, 21:491, 1933.
12. King: *South. M. J.*, 26:869, 1933.
13. Abell: *Am. J. Dig. Dis. and Nutri.*, 1:193, 1934.
14. Barnes: *Am. J. Surg.*, 20:328, 1933.
15. Kellogg: *Duodenum, Structure and Function*, P. Hoeber, 1933.

# ABSTRACTS

HUMPHREYS, E. M., AND KATO, K.

*Glycogen Storage Disease (Thesaurismosis Glycogenica) Am. Journal of Pathology, 10,5,589 (Sept., 1934).*

Glycogen storage disease, a disease first described by von Gierke in 1929, is characterized by the large size of the liver and kidneys due to the accumulation of extraordinary amounts of glycogen in the parenchyma cells of these organs. The same infiltration takes place in a less frequent number of instances in the heart. Thus has there been described a hepatomegalic or a hepatonephromegalic and a cardiomegalic type of the disease. The authors report four cases of the latter type, making a total of 15 cases of both types now reported in the literature.

The disease is a disorder of infancy and childhood. It affects both sexes and is possibly familial. It is characterized anatomically by organ enlargement and the storage of glycogen chiefly in the enlarged organs. The affected organs may attain great size and may contain glycogen in unprecedented amounts. This glycogen storage is usually not associated with degenerative or proliferative structural changes in the tissues. At least in the hepatomegalic type studies seem to point to an impairment of the mechanisms concerned in the mobilization of the glycogen and the regulation of the blood sugar as the cause. Less is known about the cardiomegalic type of the disease. In the four reported cases by the authors the hearts were 3.3 to 7 times the normal weight (infants ages 4 months heart weight 90 grams, 3 months 140 grams, 5½ months 128 grams, 8 months 260 grams respectively). The myocardial fibers were enlarged, vacuolated and in three cases filled with glycogen. In one case the liver and kidneys were similarly affected but to a lesser degree. In two cases the skeletal muscles showed vacuolar degeneration and in one of these the vacuoles contained much glycogen.

It is most commonly assumed that glycogen storage disease represents a prolongation of foetal or infantile behavior with respect to the metabolism of carbohydrates. The cause and mechanism of it are thus far, however, purely conjectural. It is an infantile disorder probably congenital and possibly familial. Most congenital or familial metabolic disorders are attributed to abnormal enzymatic functions.

N. W. Jones.

SAMUEL J. FOGELSON, M.D.

*Gastric Mucin in Treatment for Peptic Ulcer. Arch. Int. Med., Vol. 55, No. 1, January, 1935, p. 7.*

The author reports the results of the use of mucin in peptic ulcer in 555 cases of which 226 are termed intractable, i.e. not controllable by the orthodox methods of treatment. The average duration of sickness is about 8 years. Deducting 61 patients who failed to continue with treatment, the author obtained 70.5% complete relief with mucin therapy. There were 32 complete failures and the remaining were partially relieved. He obtained the most significant results in patients who had had a gastroenterostomy performed on them and later developed a recurrence of symptoms. Out of 56, 36 obtained complete relief, 16 partial and 4 obtained none whatever. The author stresses the importance of the preparation of the mucin for the patients use. These reports were made to the Committee on Mucin Therapy by physicians all over the country. A typical report sheet is shown in the text.

In his comments on mucin the author quotes extensively from recent literature in which the possible buffer action of mucin is discussed. While there seems to be consider-

able doubt as to the neutralizing effect of mucin on hydrochloric acid, or even on the depressive action on acid production, nevertheless evidence is adduced to show that mucus acts as a protective agent on the stomach, retards gastric digestion experimentally on the frog leg and inhibits the action of pepsin. The author quotes A. F. Hurst, who called attention to the deficiency of mucus in 10% of all young normal individuals in whom these factors and the presence of hyperacidity and hypertonic stomachs predispose to ulcer formation. This is a debatable question because a large number of patients with ulcer do not have hypertonic stomachs and several no hyperacidity. At the present time the manufacturers are careful to assay the products for its buffer value, test it for its secretagogue value, remove the irritating amines and the disagreeable odor and taste.

Leon Bloch, Chicago.

STACY R. METTIER, M.D., AND WILLIAM J. KERR, M.D.,  
San Francisco.

*Hepatitis and Cholecystitis in the Course of Brucella Infection. Arch. Int. Med., Vol. 54, No. 5, November, 1934, p. 702.*

Brucella infection in man is relatively a common disease in the United States. There is, however, comparatively little found concerning the visceral manifestations.

A case history is given in full, the abdominal symptoms being severe constipation, pain in the right upper quadrant, marked hyperesthesia of the skin to the right of the mid abdominal line below the umbilicus and the right costal margin. Spasm of the muscles in this region, and pain on deep palpation. A cystic mass could be felt in the region of the gall-bladder. A diagnosis of Acute Cholecystitis was made. Over a period of five weeks there was a gradual subsiding of the biliary tract symptoms, specimens of bile secured by duodenal drainage failed to show bacterial growth on culture.

At surgery, a thickened gall-bladder with adhesions to the liver and duodenum was found. In the left lobe of the liver a small round nodule 1 c.m. in diameter was removed. It was white, with central softening, and had a granular appearance.

Microscopic examination of the tissues of the gall-bladder showed an eroded mucosa, edema of the walls and early granular patches were found. Section of the liver showed the typical nodules produced in animals infected with the disease.

The culture yielded a growth of *Brucella Melitensis* from both the submucosa of the gall-bladder and the granular process in the liver. Result complete recovery.

Interpretation: In Brucellosis the continuation of the clinical picture, signs and laboratory evidences may be due to a cholecystitis and focal hepatitis.

A. H. Aaron, Buffalo, N. Y.

MABEL G. MASTEN, M. D., AND R. C. BUNTS, M.D., Madison, Wis.

*Neurogenic Erosions and Perforations of the Stomach and Esophagus in Cerebral Lesions. Report of 6 cases. Arch. Int. Med., Vol. 54, No. 6, December, 1934, p. 916.*

In 1859, Von Rokitsky described forms of softening of the stomach, frequently associated with acute affections of the brain, especially tuberculous meningitis and hydrocephalus.

Cushing, in 1932, described gastromalacia and ulcers of the upper portion of the gastro-intestinal tract definitely related to disease of the interbrain.

Six cases are presented:

(1) Abscess of the frontal lobe, terminal meningitis gastromalacia with perforation of an ulcer near the fundus on the anterior surface. Digestion of the diaphragm with pyothorax.

(2) Acute encephalitis with marked disturbance of the vegetative nervous system, multiple erosions of the stomach and perforation of the esophagus.

(3) Tumor of the posterior fossa, sexual precocity gastromalacia, perforation of the stomach and diaphragm, localized peritonitis and acute pleurisy.

(4) Infant, 14 hours old, extreme congestion of the brain; superficial necrosis of the pyloric mucosa.

(5) Tumor of the corpus callosum, anterior gastric hemorrhage, gastromalacia with a perforation near the cardia.

(6) Hypertensive cardio-vascular disease with hemorrhage into the basal ganglia, gastromalacia, esophagomalacia and rupture.

The cases seem to bear out Cushing's hypotheses of a parasympathetic center in the diencephalon where Beattie has also demonstrated a sympathetic center.

Stimulation of these centers results in softening and ulcer formation in the stomach.

A. H. Aaron, Buffalo, N. Y.

DONCHES, JOSEPH C., AND WARREN, SHIELDS.

"Chronic Cicatrizing Enteritis, with Involvement of the Caecum and the Colon." *Arch. Path.*, 18:22-29, July, 1934.

Chronic cicatrizing enteritis has also been described under the name of regional ileitis and of nonspecific granuloma of the intestine. This condition was first described by Braun in 1909, but has received increasing attention and emphasis in recent years by Mock, Crohn, and others.

The exact etiology of this condition is not known definitely. Several etiological factors have been suggested. Among these are inflammatory processes starting in the appendix, and also certain types of suture material used in abdominal operations.

The area of intestine involved is most frequently near the ileo-caecal valve, although the lesion may localize in other areas of the small intestine or colon. From the standpoint of pathology, the involved area of intestine usually presents (1) considerable thickening of the wall of the intestine with chronic inflammatory tissue, (2) ulceration of the mucosa, and (3) stenosis of the lumen. This area is also usually adherent to the adjacent structures.

The symptomatology is often vague, although frequently symptoms are present which point to partial intestinal obstruction. The presence of a palpable mass is rather frequent. Roentgen ray findings often simulate those of an obstructing malignant lesion. In fact, the chief importance of this condition lies in its mimicry of carcinoma.

The authors report a single case of particular interest because the caecum and entire ascending colon were involved without any appreciable change on the proximal side of the ileocaecal valve, other than muscular hypertrophy of the wall of the terminal ileum and dilatation. These changes were due obviously to the caecal obstruction. At operation a mass of chronic inflammatory tissue

and fat was found surrounding the caecum. This was thought at the time to be carcinoma. The ascending colon was markedly thickened and shortened, with a constricted lumen and a partially eroded mucosa. The terminal ileum, caecum, ascending colon and proximal part of transverse colon were resected. On microscopic examination the mucosa of the caecum and ascending colon was atrophic where present. It showed metaplasia of the epithelium, but no malignant change. The deeper layers showed extensive fibroblastic proliferation, edema, and infiltration with polymorphonuclear leukocytes, lymphocytes, plasma cells and eosinophils. The appendix appeared to be buried in the mass of chronic inflammatory tissue surrounding the caecum. (The history of previous, repeated attacks of "abdominal cramps" in this patient suggested probable mild attacks of appendicitis).

The authors also review briefly twenty-four cases of chronic cicatrizing enteritis found in the literature.

James I. Baltz, Detroit.

BEAVER, DONALD C.; HENTHORNE, JOHN C., AND MACY, JOHN W.

"Abscesses of the Liver Caused by *Bacteroides Funduliformis*." *Arch. Path.*, 17:493-509, April, 1934.

Two cases of hepatic abscesses caused by *Bacteroides funduliformis* are presented. The previous literature upon this type of infection is also reviewed. The genus *Bacteroides* includes certain anaerobic, non-sporulating bacilli. Seventeen species have been listed, some of which are gram-positive and others gram-negative, some motile and others nonmotile. *Bacteroides* are normal inhabitants of the intestinal tract of man.

*Bacteroides* infection may lead to serious suppurative and gangrenous lesions in man. Primary lesions occur most frequently in the large intestine and in the genito-urinary tract. Colonic lesions usually originate either in infected carcinomas or in the crypts. Direct hematogenous dissemination of the infection from the colon to the liver may develop, leading to hepatic abscess formation. Primary lung lesions may also occur, usually upon the basis of aspirated infection. Pulmonary lesions may consist of septic infarcts, patches of bronchopneumonia, or putrid, gangrenous abscesses of variable size.

The clinical syndrome of *Bacteroides* infection is that of an extreme degree of sepsis, with a high, remittent type of fever, chills, perspiration, and exhaustion. The physical findings will vary with the localization of the lesions.

In the first case reported by the authors, at autopsy the primary lesion consisted of an infected ulcerating carcinoma of the rectum. Certain of the adjacent veins were invaded by carcinoma, and also contained infected thrombi. Abscesses of the liver were found in close association with carcinomatous metastases of the liver. Portal thrombosis was present.

In the second case large, multilocular, hepatic abscesses were found, confined within the right lobe of the liver, and suggesting dissemination by way of the portal circulation. It is probable that the hepatic abscesses in this case arose from a cryptic focus somewhere in the large intestine.

The authors review the detailed pathological and bacteriological findings in these two cases, as well as the results of animal tests for pathogenicity of the organisms.

John G. Mateer, M.D.

## SECTION II—*Experimental Physiology*

### Studies on the Neutralization of Gastric Acidity: Ewald Test Meal and X-ray (Barium Meal) Studies in Patients with Duodenal Ulcer, Gastro-jejunostomy and Gastric Resection

By

ROBERT ELMAN, M.D.

ST. LOUIS, MISSOURI

and

J. WENDELL MacLEOD, M.D.

MONTREAL, CANADA

THE acidity of gastric contents as a factor in the pathogenesis and treatment of peptic ulcer, particularly of the duodenum, has long been considered of great importance. Clinical study of acidity has been, to a great extent, disappointing, due largely to the wide variations in acidity which are found in gastric contents both of normal and diseased patients as shown by Keefer and Bloomfield (1) in spite of the trial of many types of stimuli or test meals to evoke secretion. This lack of uniformity has not only discouraged its clinical use in estimating normal secretory function, but has detracted from its diagnostic value in indicating pathological changes. As a consequence, greater reliance has been placed in recent years on studies of gastric morphology and motor function as revealed by the x-ray after ingestion of a barium meal.

The present study is an attempt to investigate the acid factor by means of a relatively new functional test. Instead of measuring the acid secreted in response to a stimulus it will be concerned with the neutralization of acid introduced in solution directly into the stomach. The findings obtained will be compared with the results of the usual fractional Ewald test meal and both will then be correlated with the

clinical picture in each case and also with the observations made in the dark room from fluoroscopic study after the ingestion of barium.

The theoretical basis for the use of a neutralization test in the study of gastric acidity is twofold. The acidity of stomach contents obtained after a test meal, first of all, is not that of gastric juice secreted as such, but is the resultant of secretion and neutralization. This is apparent from the fact that pure gastric juice as actively secreted both in animals and in the human being (2) is of a high and constant acidity (i.e. .5% HCl or 135 degrees) whereas, as observed clinically in the normal individual it rarely goes above half this figure. Whether it is food, mucus, neutral chloride or regurgitated alkaline pancreatic juice which is responsible for this neutralization is another problem; suffice it to say that whatever it is the rôle it plays in governing and regulating gastric acidity, though important, is one which escapes direct estimation in the ordinary test meals. A second reason for the use of a neutralization test is that one is not always sure that test meals really test; that is, that the stomach has actually been stimulated by the method designed to do so, or that, even if the test has evoked a secretory response, the effect is of a magnitude approaching normal function. To do so one should really

\*From the Departments of Surgery and Medicine, Washington University School of Medicine and Barnes Hospital, St. Louis, Missouri. Submitted January 1, 1935.

CHART I

*Duodenal Ulcer with Symptoms (X-ray Positive)*

| Case | Sex and Age | Symptoms                                                                            | X-ray Findings |                                      |                   |                          |
|------|-------------|-------------------------------------------------------------------------------------|----------------|--------------------------------------|-------------------|--------------------------|
|      |             |                                                                                     | Residual Fluid | Duodenal Cap                         | Tenderness at Cap | Emptying Time            |
| 2    | M 28        | Epigastric pain 1 hr. after eating relieved by food.                                | 1° +           | Deformed                             | —                 | 3½ hours                 |
| 3    | F 35        | Epigastric pain 1 hr. after eating relieved by food.                                | 0              | Small contracted                     | 0                 | 6 hour retention         |
| 7    | M 48        | Slight pain and indigestion relieved by powders.                                    | 0              | Elongated and transverse; deformity? | 0                 | 2 hours                  |
| 8    | M 35        | Pain relieved by powders.                                                           | 0              | Redundant and deformed (?)           | ?                 | 3 hours                  |
| 9    | M 65        | Severe pain relieved by food.                                                       | 0              | Slight deformity                     | +                 | 1½ residue at 4 hours    |
| 11   | M 55        | Severe pain relieved by powders.                                                    | 1° to 2°       | Deformed; irritable                  | ++                | 6 hour retention         |
| 12   | M 56        | Severe pain and vomiting.                                                           | 2°             | Clover leaf deformity                | 0                 | 4 hours                  |
| 15   | M 30        | Epigastric pain 1 hr. after eating relieved by food. Also indigestion and vomiting. | 1° to 2°       | Difficult to visualize; deformity?   | 0                 | 3 hours (slight residue) |



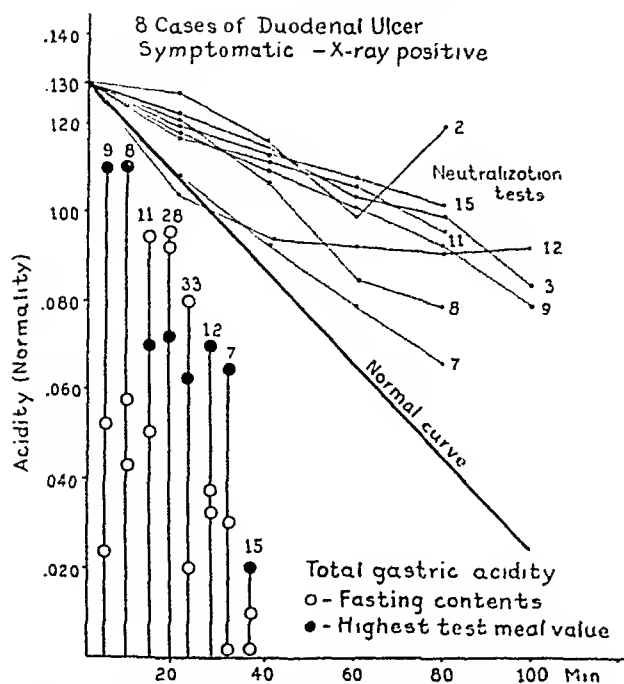


Fig. 1. Composite graph of neutralization tests in patients with symptomatic duodenal ulcer confirmed by x-ray study. Note incomplete neutralization as compared with normal. Clinical details are recorded in Chart I. The vertical lines represent the acidity of gastric contents both fasting and secreting, the latter representing the highest value obtained after administration of the test meal. See Chart I).

allow the patient to eat a regular meal under normal circumstances before measuring the resulting acidity. With the neutralization test consideration of the secretory response is excluded for the acid is introduced at once; only the single mechanism of neutralization is measured. This is not entirely so for the introduction of fluid of any kind by mechanical distensions of the stomach wall has been shown to constitute a gastric stimulus. (3) In this case the amount of fluid used is small (300 cc.) and the magnitude of the stimulus is thus very slight.

#### PREVIOUS OBSERVATIONS

Migai, (4) in 1909, was probably the first to introduce acid gastric juice from a dog and also HCl solutions into the human stomach and he found that neutralization thereof proceeded rapidly and completely. Boldyreff, however, was really responsible for the use of such a test solution of acid in experiments designed to measure the acid regulating power of the stomach which he claimed occurred normally because of the regurgitation largely of alkaline pancreatic juice into the stomach (5). Spence, Meyer, Rehfuess and Hawk (6) furthered the theory of Boldyreff by many studies, some of which involved the introduction of 100 cc. of .4% HCl (110 degrees) into the human stomach. They, too, found that it was promptly neutralized. Apperly (7), in 1926, introduced 400 cc. of a weaker acid solution (.3 to .35% HCl or 80 to 100 degrees) into the stomach and observed the same effect. MacLean and Griffiths (8) used similar acid test meals for functional studies of gastric physiology. Palmer (9) introduced 50 cc. of stronger HCl solution (135 degrees), but did not study its neutralization; he noted only its effect on the reproduction of symptoms. In addition to these clinical studies acid solutions have been given to animals by many observers including, besides Boldyreff, Burget and Steinberg (10), Mathews and Dragstedt (11),

Elman (12) and Olch (13). Its behavior in the normal dog's stomach was the same as that in the normal human stomach; that is, the acidity was rapidly and promptly neutralized. In general, however, in all of these studies the use of the acid solution was incidental to a special problem; its use in obtaining functional and diagnostic data was not investigated.

Apperly and Cameron (14), in 1923, proposed and used a test solution of 250 cc. of .4% HCl (110 degrees) as a measure of the neutralizing (alkali producing) power of the pancreas, since they assumed that neutralization was due to regurgitation of alkaline pancreatic juice. The first to study peptic ulcer cases with the acid neutralization meal was one of the present authors (R.E.). A definite delay in the neutralization of the acid solution over the normal was noted (15) in twelve cases of proved duodenal ulcer. After gastroenterostomy, moreover, this mechanism was accelerated so that the acid solution introduced was neutralized much more rapidly even than in normals. More recently J. L. Levy (16) used the same test in a series of patients with pyloro-duodenal disease and presented data which pointed to its definite value as a diagnostic test which seemed more uniform than single acid values obtained 45 minutes after giving an Ewald meal and more closely related to the clinical picture and x-ray findings.

#### METHODS

A group of unselected patients with a diagnosis of duodenal ulcer was obtained from the gastro-enterological clinic of Washington University; of those under medical treatment with definite x-ray evidence of ulcer most were studied at a time when they were having definite symptoms; a few, however, were entirely free of symptoms. Then there were patients in whom a gastro-enterostomy had been done for duodenal ulcer which was verified by operation. A few patients with gastric resection were also studied. They had had gastric ulcers (one had a gastric carcinoma). All the operated patients were symptom free. With the exception of three patients (Cases 23, 24 and 25) months or years had elapsed since operation.

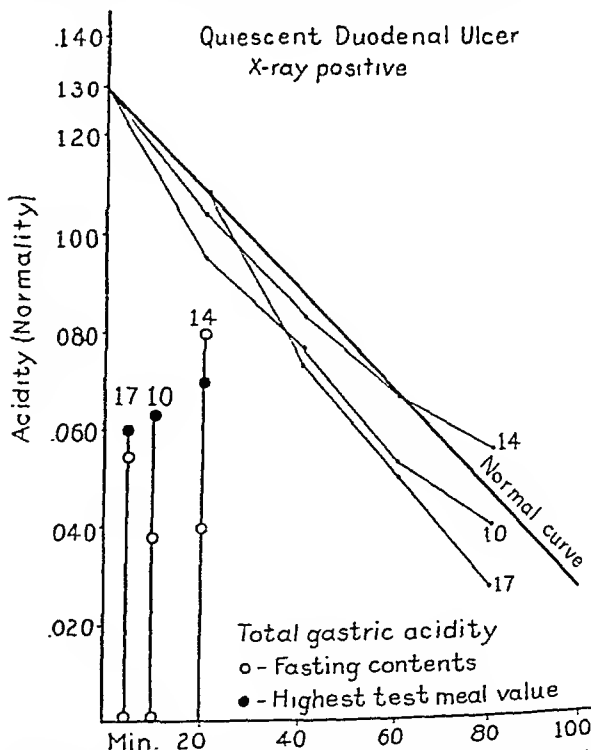


Fig. 2. Note normal neutralization curves in patients with duodenal ulcer as shown by x-ray but who are having no symptoms. (See Chart II).

Finally three patients who had symptoms of duodenal ulcer, were found to show no x-ray evidence thereof; they were kept in a separate group. Observations, however, were made without regard to these groupings.

The routine examinations were made as follows: At the first visit a barium meal was given and the patient studied fluoroscopically until the stomach was empty; at the second visit the neutralization test was done; at the third visit a fractional test meal was carried out. Most of the patients were subjected to these observations at intervals of one week between visits. The usual preparation of fasting before each examination was made. For the

will be briefly summarized below and discussed in more detail further on.

Several "normal" patients with normal neutralization curves were studied, but are not shown since they agree with those already reported in a previous observation (15). That they show a rather uniform regularity has also been confirmed by Levy (16). The solid line used in each test figure as the normal was obtained from the communication already mentioned (15). This same "normal" curve was noted in three patients with history and x-ray evidence of duodenal

CHART II

*Duodenal Ulcer Without Symptoms. (X-ray Positive)*

| Case | Sex and Age | Symptoms           | X-ray Findings |                                          |                   |               |
|------|-------------|--------------------|----------------|------------------------------------------|-------------------|---------------|
|      |             |                    | Residual Fluid | Duodenal Cap                             | Tenderness at Cap | Emptying Time |
| 10   | M 40        | None               | 1°             | Medial border deformed; quick irritable. | 0                 | 5½ hours      |
| 14   | M 35        | None               | 0              | Quick; irritable; deformity?             | 0                 | 5 hours       |
| 17   | F 42        | Slight indigestion | 0              | Small and slightly deformed?             | 0                 | 3½ hours      |

x-ray a barium meal was made with 400 cc. of buttermilk plus 120 gm. of barium sulphate. Many of the patients had in addition serial x-ray studies which included films. Shredded wheat biscuit and 400 cc. of water were used for the Ewald test meal and 300 cc. of .5% HCl (135 degrees) for the neutralization test as described in detail previously (15).

## FINDINGS

On the basis of the clinical picture the 25 patients fell into the groups as mentioned above: (1) Symptomatic ulcers—8 cases; (2) quiescent ulcers—3 cases;

ulcer (presumably healed), but who were having no symptoms even though they were taking no special treatment see (Chart 2 and Fig. 2).

Of the other patients, Group 1 contained eight ulcer cases who were having symptoms (some in spite of medical treatment, many on no treatment at all). They all showed delayed curves indicating faulty acid neutralization. Some also showed marked retention (not shown in the figures). The third and fourth groups comprise those operated on and as can be seen (Figs.

CHART III

*Duodenal Ulcer; Gastroenterostomy*

| Case | Sex and Age | Symptoms               | X-ray Findings                                        |                           |                   |                                     |                                                          |
|------|-------------|------------------------|-------------------------------------------------------|---------------------------|-------------------|-------------------------------------|----------------------------------------------------------|
|      |             |                        | Residual Fluid                                        | Duodenal Cap              | Tenderness at Cap | Emptying Time                       | Stoma                                                    |
| 1    | M 40        | Occasional hunger pain | 0                                                     | Patent, but narrowed      | 0                 | 2½ hrs.                             | Clearance mostly; by stoma in distal pars media.         |
| 4    | M 32        | None                   | 0                                                     | Not canalized             | —                 | 3½ hrs. (almost empty at 2 hrs.)    | Clearance entirely by stoma in distal pars media.        |
| 5    | M 47        | None                   | 0                                                     | Small, no deformity       | 0                 | 2½ hrs. (almost complete at 2 hrs.) | Clearance chiefly by stoma in pars prepylorica.          |
| 6    | M 50        | None                   | 0                                                     | Canalized but slightly    | 0                 | ¼ residue at 3 hrs.                 | Clearance chiefly by stoma, slightly high in pars media. |
| 16   | M 31        | None                   | 0                                                     | Slight clearance narrowed | 0                 | ¼ residue 2 and 2½ hrs.             | Clearance only partly by stoma, lying high and proximal. |
| 24   | M 55        | None                   | 16 days after operation (same as Case 11 in Chart 1). |                           |                   |                                     |                                                          |
| 25   | M 75        | None                   | 17 days after operation.                              |                           |                   |                                     |                                                          |

(3) postoperative gastro-jejunostomies—7 cases; (4) gastric resections—4 cases; and (5) syndrome of ulcer without x-ray evidence—3 cases. Details of their clinical features and x-ray findings are presented in Charts 1 to 5; the acidity studies are represented in corresponding Figures 1 to 5 which show composite graphs of the acid neutralization curves as well as the titration values of both fasting contents and the highest point reached during the test meal. These charts are largely self explanatory. The findings, however,

3 and 4) the neutralization of the acid is more accentuated than normal; this is especially true of the gastric resections. A secondary rise in acidity of three of the patients with gastro-enterostomy is of special interest and will be discussed later. The three patients with duodenal ulcer symptoms (Group 5) all showed delayed curves even though the x-ray showed no positive evidence of ulcer.

Three acid values are shown in the text figures; two represent the fasting contents obtained before



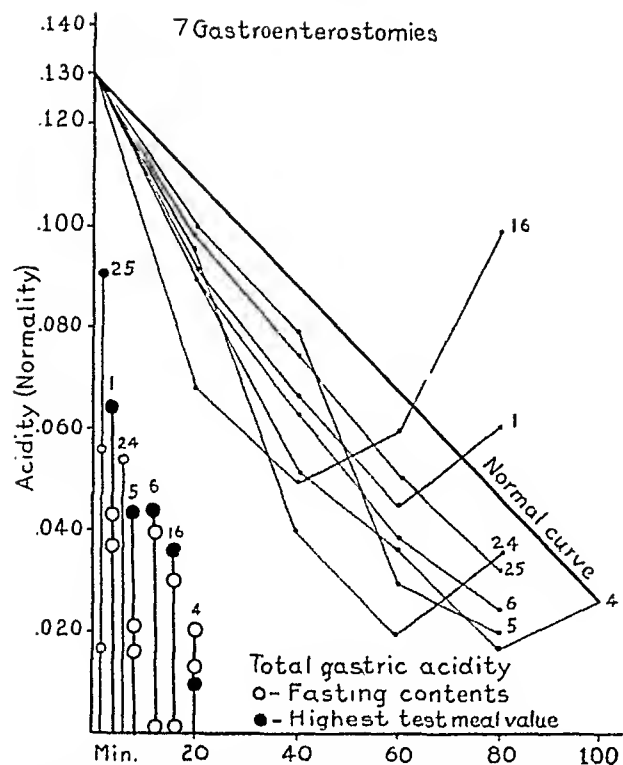


Fig. 3. Note the more rapid neutralization than normal in patients with gastroenterostomy. The terminal rise of the curve in three cases is discussed in the text. (See Chart III).

starting the Ewald and the neutralization test. The third value is the highest acid titration from the fractional aspirations obtained after giving the shredded wheat biscuit. It will be seen that by comparing the two fasting values there is considerable variation in individual cases. The highest acid values also vary in each group, not only between each other, but also when compared with the results of the neutralization test. Moreover, in a number of cases the fasting acid value was greater than that reached after the test meal.

The results of the x-ray study are shown in the charts and comprise information as to the emptying time, appearance of, and tenderness over the cap, residual fluid and activity and appearance of the stoma (in the operated cases).

#### COMMENT

The importance of the findings recorded herein lies in the fact that they point to the usefulness of a test for measuring the rate of neutralization of acid within the stomach. The series of cases, though small, yielded fairly uniform results. The value of the test may be best considered (1) by comparing it as a measure of the behavior of gastric acidity with the results of the fractional test meal and (2) by comparing it as an indication of gastric functional disability with the x-ray findings and the clinical picture.

That the neutralization test should give a better estimate of the behavior of gastric acidity than study of gastric contents obtained following the use of an Ewald test meal has been suggested on the basis of the theoretical considerations already mentioned. Actually the findings bear out this contention as perusal of the various charts and test figures will show.

This is particularly true of Group 1. While it will be seen that the test meal acidity is in general high in these ulcer cases with symptoms (Fig. 1) there are notable exceptions. Thus, Case 15 had subnormal acid values of 0°, 10° and 20°, yet the neutralization test showed a high level of acidity indicating a faulty neutralization which agreed rather well with the severe symptoms this patient had (Chart 1). Two of the cases (No. 7 and 12) had acid values in the upper level of normal and only two had really high values above 100° (Cases 8 and 9), yet the neutralization curves all showed delay in the neutralization of the acid test solution.

Of much interest were the cases with gastro-enterostomy (Chart 3). In them the test meal acidities were within relatively normal limits (Fig. 3). The neutralization test, on the other hand, showed a reduction of gastric acidity more rapid than normal; this agreed with the findings already reported in another series of cases (15) and reflects perhaps the beneficial physiological effects of the operative procedure. The terminal rise of the curve in cases 1, 4 and 16 were of special interest; it did not occur in previous observations (15). One of them (Case 1) was beginning to have mild symptoms (slight hunger pains relieved by food). The patient with the most marked terminal rise (Case 16) showed under the fluoroscope (see Chart III) a stoma which was high and proximal, a poor position for a gastroenterostomy, through which clearance was poor. This is the only patient with such a finding; it suggests that the presence of the terminal rise in the neutralization curve may be connected with an inadequate function of the stoma. On the other hand a slight terminal rise was noted in one unoperated patient (case 2 of the first group). Further observations will have to be made.

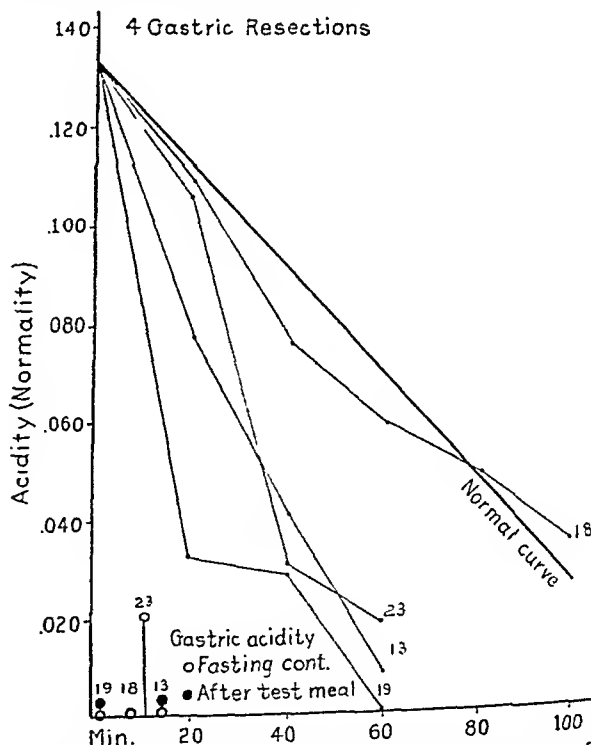


Fig. 4. Note the very rapid neutralization in all but one of the above curves obtained from patients with gastric resection. (See Chart IV).

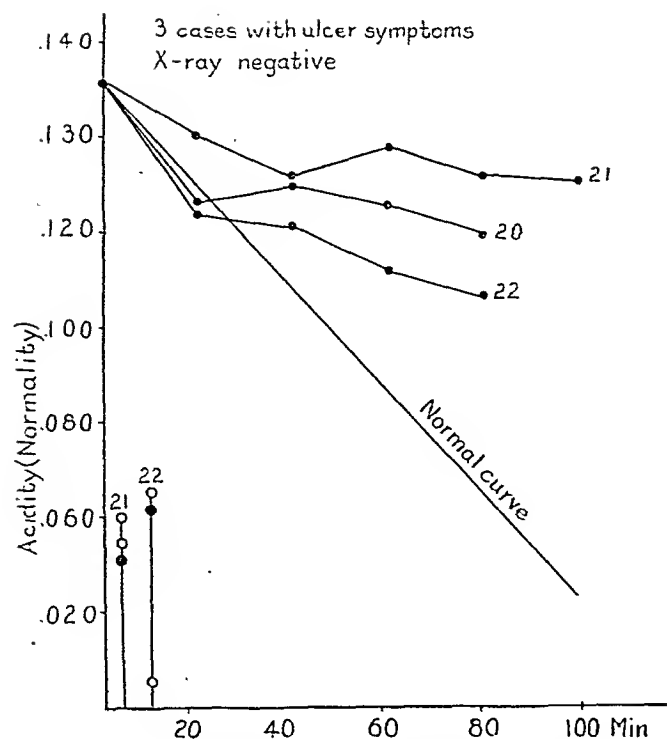


Fig. 5. Note the incomplete and almost absence of neutralization in patients with characteristic ulcer symptoms but who showed no direct evidence of ulcer by x-ray. (See Chart V).

In the gastric resections (Fig. 4) the fasting and test meal acid values were all close to zero. While three of them showed very rapid neutralization rates it is of interest to note that one of them showed a rather normal curve (Case 18). In the final Group 5, the Ewald test meal was only done in two of the three cases. It is suggestive that in both the results were within normal limits, even though the symptoms were marked and the neutralization test showed a high level i.e. faulty neutralization, similar, in fact, to the cases with definite x-ray evidence of ulcer in Group 1.

Another finding worthy of note was the fact that the acid values of the fasting contents were not infrequently higher than the highest figures obtained after the test meal of shredded wheat biscuit (see Cases 2, 3 and 11 in Fig. 1; Case 14 in Fig. 2; Case 4 in Fig. 3; and Case 21 and 22 in Fig. 5). This bears out one of the theoretical objections (mentioned above) to the usual form of gastric analysis; that is, that the stimulus designed to provoke secretion does not always do

so the acidity of the fasting contents in these cases was so, or that it falls short of what occurs normally. That higher indicates that the test meal failed to provoke a really active secretion for it would be inconceivable that an organ would secrete more while fasting than while working.

As an indication of functional disability the neutralization test seems of especial value in that the findings after its use agreed with the clinical picture as well as, and in many cases better than, the results of x-ray investigation. Thus, in Group 1, the patients with the worst symptoms had the highest acid curve; that is, most faulty neutralization (Cases 12 and 15), yet the x-ray in both of these cases showed no retention and no tenderness over the cap. The case with the mildest symptoms (Case 7) had a curve which approached the normal closer than any of the others; in this case the x-ray also reflected the relative mildness of the lesion. In the three cases of Group 2 the evidence of ulceration by x-ray was definite, yet the neutralization curve was normal; the absence of symptoms in these patients suggested perhaps that the ulcers were healing. On the other hand, in the three patients of Group 5 the neutralization test showed faulty neutralization, the curve being similar to those of the patients with definite ulceration, and indeed they were having classical ulcer symptoms. Yet x-ray showed no positive evidence of an anatomical lesion. It is suggestive, however, that in these patients gastric residual fluid and gastric retention were noted by x-ray and one showed a "quick" cap which, however, later showed perfect contour. Very likely these patients had a perversion of function (pylorospasm?) which leads to ulceration; the neutralization test, thus, would seem to indicate rather early evidence of disease. Such patients may be on their way toward the formation of an ulcer later. Many, however, clear up under medical treatment and two of the three patients in this group were getting relief. More of them will be studied and reported later, particularly as to the effect of symptomatic relief on the neutralization test.

#### SUMMARY

1. Gastric studies of 25 patients were made by means of x-ray (after a barium meal), fractional Ewald test meals and neutralization curves of gastric acidity. The patients comprised those with x-ray evidence of ulcer, both with and without symptoms, those with symptoms of ulcer but with negative x-ray findings, and those with gastro-enterostomies and gastric resections.

CHART IV  
Gastric Resection

| Case | Sex and Age | Symptoms | X-ray Findings                                    |                |            |               |
|------|-------------|----------|---------------------------------------------------|----------------|------------|---------------|
|      |             |          | Residual Fluid                                    | Stoma          | Tenderness | Emptying Time |
| 13   | F 30        | None     | 0                                                 | Functions well | 0          | 2 hours       |
| 15   | F 28        | None     | 0                                                 | Functions well | 0          | 2 hours       |
| 19   | F 45        | None     | 0                                                 | Functions well | 0          | 3 hours       |
| 23   | M 60        | None     | 14 days after operation for carcinoma of stomach. |                |            |               |

2. The findings obtained by means of the neutralization test suggest that it is a more useful method of studying gastric acidity than is the Ewald fractional test meal since it gives more uniform results.

3. As an indication of perverted function the neutralization test shows closer agreement with the clinical picture in many cases than with other tests including the x-ray.

CHART V  
*Ulcer Symptoms (X-ray negative)*

| Case | Sex and Age | Symptoms                                                                          | X-ray Findings |                                                        |                   |                 |                           |
|------|-------------|-----------------------------------------------------------------------------------|----------------|--------------------------------------------------------|-------------------|-----------------|---------------------------|
|      |             |                                                                                   | Residual Fluid | Duodenal Cap                                           | Tenderness at Cap | Emptying Time   | Remarks                   |
| 20   | M 19        | Definite epigastric pain before meals and at night relieved by food.              | 1°             | Normal.                                                | 0                 | 6 hour residue. | Improved on medical care. |
| 21   | F 30        | Epigastric pain after meals relieved by food.                                     | 1°             | Bulb quick and small but later showed perfect contour. | 0                 | 6 hour residue. | —                         |
| 22   | M 28        | Nervousness and epigastric pain 1½ hours after eating, relieved by food and soda. | —              | Irritable; perfect contour.                            | 0                 | —               | Improved on medical care. |

### REFERENCES

1. Kiefer, C. S., and Bloomfield, A. L.: *Am. J. Med. Sc.*, 1927:173:460.
2. Carlson, A. J.: *Am. J. Physiol.*, 1915:33:248.
3. Lina, R. K. S., Ivy, A. C., and McCarthy, J. E.: *Quart. J. of Exp. Physiol.*, 1925:15:13.
4. Mingai, 1909, quoted by Boldyreff.
5. Boldyreff, W.: *Erg. d. Physiol.*, 1911:11:121. *Quart. J. Exp. Physiol.*, 1914:8:1.
6. Spencer, W. H., Meyer, G. P., Rehfuess, M. E., and Hawk, P. B.: *Am. J. Physiol.*, 1916:39:459.
7. Apperly, F. E.: *Brit. J. Exp. Path.*, 1926:7:111.
8. McClellan, H., and Griffiths, W. J.: *J. of Phys.*, 1928:66:356.
9. Palmer, W. L.: *J. A. M. A.*, 1927:88:1778.
10. Burget, G. E., and Steinberg, M. E.: *Am. J. Physiol.*, 1922:60:308.
11. Matthews, W. B., and Dragstedt, L. R.: *Surge, Gyn. and Obst.*, 1932:55:265.
12. Elman, R.: *Arch. Surg.*, 1928:16:1256.
13. Elman, R., and Rowlette, A. P.: *Arch. Surg.*, 1931:22:426.
14. Elman, R., and Eckert, C. T.: *Arch. Surg.*, 1934:29:1001.
15. Olch, I. Y.: *Arch. Surg.*, 1928:16:125.
16. Apperly, F. E., and Cameron, G.: *Med. J. Austral.*, 1923:1:521.
17. Elman, R.: *Surge, Gyn. and Obst.*, 1929:49:31.
18. Levy, J. L.: *Ann. Int. Med.*, 1934:7:1244.

## ABSTRACTS

REIFENSTEIN, EDWARD C., AND ALLEN, ELLERY G.

*The Treatment of Chronic Hemolytic Jaundice With Liver Extract. J. A. M. A.*, 103:6068 (December 1, 1934).

Splenectomy has long been considered to be the most successful accepted therapeutic procedure in the treatment of chronic hemolytic jaundice. The fragility of the erythrocytes persists after operation and hemolytic crises have recurred in some cases.

Because of these occasional failures and because the patients readily die from the disease, some clinicians have adopted a conservative attitude in its treatment.

Liver extract was used by various authors in some of these cases. The results, as gleaned from the literature, have been conflicting. For this reason the authors felt that further studies as to the value of liver therapy in chronic hemolytic jaundice was justified. They cite three cases of chronic hemolytic jaundice treated with liver extract, all of them showed clinical improvement. In one case, clinical improvement occurred but the increase of icteric index, urobilinuria, and increased fragility of erythrocytes persisted, while the anemia improved. The other two cases showed no definite or sustained increase in fragility of the red cells, though similarly treated, but the disappearance of a mild anemia, jaundice, and urobilinuria were noted.

Francis D. Murphy, Milwaukee, Wis.

PEARSE, H. E.

*Experimental Chronic Intestinal Obstruction from Blind Loops, S., G., and O.*, 59:726, 1934.

On 60 dogs the author studied the fate of blind loops after jejunal enteroanastomosis and obstruction. The results were as follows:

1. That portion of bowel below the obstruction where the peristaltic action was directed away from the blind end toward the anastomosis remained empty.

2. In the segment above the obstruction where the peristaltic current was from the anastomosis toward the blind end, material was carried into and retained in the blind segment. If this loop was one foot or less, it emptied itself and did not become dilated. If this blind loop was two feet long, it became dilated and filled with inspissated material. This, however, caused no symptoms. If this blind loop was three or four feet long, enormous hypertrophy and dilatation followed. If perforation did not occur, chronic intoxication resulted after 3 or 4 months. Resection of this blind loop allowed complete recovery of the animal. Blind loops five or six feet long subtracted such a large part of the total intestinal length that the majority of the animals died from inanition and dehydration.

K. Hosoi, New Orleans.

## SECTION III—Nutrition

### Glycosuria and Lactosuria of Pregnant and of Lactating Women

By

HENRY J. BROCK, M.D.

and

ROGER S. HUBBARD, Ph.D.

BUFFALO, NEW YORK

**D**URING the last 75 years interest has been taken in the excretion of sugar by women during pregnancy and lactation. It has long been known that lactosuria occurs in these conditions, but exact study has been greatly hampered by a lack of suitable analytical methods. In the present communication, a method capable of demonstrating lactose in concentrations as low as 5 to 10 mg. per 100 cc. will be described, and the results of its application to a series of urine specimens from pregnant, lactating, and normal women will be discussed.

#### HISTORICAL RESUME

Blot (1), (1856), found a reducing substance in the urines of 50 per cent of the gravid and nursing women whom he studied, and Hofmeister (2), (1877), showed that the substance present was lactose. Since that time much work has been done, and many methods for studying the sugar quantitatively have been developed. A complete review of this literature will not be attempted here. Instead, a few of the more recent papers will be discussed; readers are referred to the bibliographies of these for further detailed information.

Snock (3) has relied chiefly upon the formation of the osazone, and has used fermentation with yeast as a corroborative analytic method in some instances. This method cannot be applied accurately when lactose is present in concentrations lower than 0.1 per cent; especially is it unsatisfactory when a mixture of sugars is present. Winter (4, 5) abandoned this procedure, and substituted one based upon the specific rotation, melting point, and solubility of glucose and of lactose. His methods served to identify the sugars, but gave only approximate estimations of the amounts present. Kowarski (6), Gootz and Tunger (7), and others have determined the reducing power of untreated urine, and have repeated the analyses after hydrolysis. By such a technique it is difficult to distinguish one polysaccharide from another, for all may cause similar increases in reducing power after they have been hydrolyzed. Kleiner and Tauber (8) recently have described a rather simple and practicable

procedure. Using appropriate copper reagents, they determine the total reducing sugars and the monoses in urine. The authors did not determine amounts of sugar which were present in concentrations lower than 0.05 per cent, and they did not differentiate various disaccharides from one another when more than one sugar of this type was present. Castellani (9, 10, 11) and others (12) have demonstrated lactose in urine by differential fermentation with yeasts and organisms. 0.05 per cent was the lowest concentration they could demonstrate by the technique which they used. Harding (13, 14, 15, 16) and his co-workers used a somewhat similar procedure for showing the presence of lactose in urine or in a mixture of sugars. Hubbard and Kingsbury (17) combined Castellani's bacteriological fermentation with the blood sugar method of Folin and Wu (18), and were able to determine lactose quantitatively when it was present in blood in concentrations as low as 0.005 per cent. The method which we have used for determining lactose in urine is based upon similar principles.

#### DESCRIPTION OF ANALYTIC METHOD

**Apparatus:** (1) 50 cc. beakers. (2) Small watch glasses to cover beakers. (3) Folin-Wu sugar tubes. (4) 1 cc. pipettes calibrated in gradations of 0.01 cc. (5) Sterile 1 and 2 cc. pipettes. (6) 3 cc. pipettes. (7) Sterile, cotton-plugged 15 cc. centrifuge tubes. (8) Sterile agar slants in 6 in. test tubes. (9) Incubator.

**Reagents:** (1) Heavy suspension of *B. Coli* and *B. Proteus*. These suspensions are made in the following way: agar slants are heavily inoculated with organisms and incubated for 24 hours; 2 cc. of sterile distilled water then is poured over each slant with sterile 1 cc. pipettes; the organisms thus are freed from the surface of the agar and suspended in the water by the aid of a sterile platinum loop; the suspensions should be used at once. The *B. Coli* ferment all the common sugars (glucose, fructose, lactose, galactose, maltose, xylose, arabinose) and *B. Proteus* ferments all except lactose and xylose. Differential fermentation with these organisms therefore furnishes a method for determining lactose and xylose, even when they are present only in traces, in a solution containing very large amounts of other sugars. Since xylosuria apparently does not occur (Foot-note 1), the organisms can be used for determining lactose in urine.

(1) Formerly it was believed that xylose was excreted in most cases of pentosuria. Recent investigations have shown that the sugar present in this condition is xylo-ketose, which does not interfere with the method described as it is not fermented by *B. coli*.

\*Preliminary report was read before the Buffalo Pathological Society in November, 1934.

†From the Buffalo General Hospital and the University of Buffalo Medical School, Buffalo, New York.

Submitted December 7, 1934.

(2) Dinitrosalicylic acid solution (Sumner 19) "To 300 cc. of 4.5 per cent carbonate-free sodium hydroxide add 880 cc. of 1 per cent dinitrosalicylic acid and 255 gms. of Rochelle salt ( $\text{KNaC}_4\text{H}_4\text{O}_6 \cdot 4\text{H}_2\text{O}$ ), mix until dissolved, and keep tightly stoppered. Dinitrosalicylic acid can be prepared as described in a previous paper (20) or can be obtained from Eimer and Amend or from the Eastman Kodak Co."

(3) Standards. Dissolve 0.800 gms. of lactose in a liter of distilled water. One cc. of this solution contains 0.0008 gms. (0.8 mg.) of lactose.

**Method:** Place approximately 10 cc. of urine in a 50 cc. beaker (Foot-note 2). Cover with a watch glass and boil for two minutes to sterilize. The following procedures should be carried out with precautions which will insure the preservation of sterility: Pipette 2 cc. of urine into each of 3 cotton-stoppered 15 cc. centrifuge tubes. Add 0.5 cc. of a heavy suspension of *B. Coli* to the first tube, 0.5 cc. of a similar preparation of *B. Proteus* to the second, and 0.5 cc. of sterile distilled water to the third (control) tube. The same pipette can be used for 6 or 8 inoculations with the same organism, but precautions must be taken to avoid mixing the cultures. Incubate for 12 to 16 hours at 38° C. After incubation sterile precautions need not be taken. Dilute the contents of each tube to 3 cc. with distilled water. Mix. Centrifuge if cloudy. Measure 1 cc. of the contents of each tube into a Folin-Wu blood sugar tube. Prepare standards by measuring 1, 0.5, 0.25, and 0.125 cc. of the standard lactose solution, containing respectively 0.8, 0.4, 0.2, and 0.1 mg. of lactose, into Folin-Wu sugar tubes. Add to each standard enough water to give a total volume of 1 cc. To each of the sugar tubes containing standards and aliquots of urine add 3 cc. of

the dinitrosalicylic acid solution. Immerse the tubes in a boiling water bath for 5 minutes. Cool. Dilute the contents of all tubes to 25 cc. Mix. Compare the color of each of the unknown solutions with that of the standard nearest to it in tint in a colorimeter.

**Calculation:** The reducing power of the contents of each tube is calculated by means of the following formula:

$\frac{\text{reading standard}}{\text{reading unknown}} \times \text{value of standard} \times 1.5 \times 100 = \text{mg. reducing substances in 100 cc.}$  If the urine was diluted before it was analyzed, the results must be multiplied by a factor to correct for the degree of dilution. By this calculation all results are given in terms of the lactose equivalent to the reducing substances present. To find the amounts of the different sugars calculate as follows:

The color in tube A is due to residual (non-sugar) reducing substances.

The color in tube B is due to residual reducing substances + lactose.

The color in tube C is due to residual reducing substances + lactose + other fermentable sugars (glucose).

Tube "A" is the one treated with *B. Coli*, tube "B" the one inoculated with *B. Proteus*, and tube "C" the control tube.

mg/100 cc. reducing substances in B — mg/100 cc. reducing substances in A = mg. lactose per 100 cc. urine.

mg/100 cc. reducing substances in C — mg. 100 cc. reducing substances in B = mg. other (non-lactose) fermentable sugar per 100 cc. urine. "Other sugars" are given in terms of lactose by this calculation.

The result can be converted into terms of glucose, which is the sugar almost always determined, by multiplying by the factor 100/124 for both Sumner (19) and the authors have found that 124 mg. of lactose gives the same color as 100 mg. of glucose when dinitrosalicylic acid is used for determining the sugars.

By the method described, amounts of lactose as great as 200 and as small as 5 mg. per 100 cc. of urine

TABLE I  
Concentrations of sugars in urine

| Lactose.                                                         |             |         |          |          |          |          |          |          |            |            |            |            |            |                    |
|------------------------------------------------------------------|-------------|---------|----------|----------|----------|----------|----------|----------|------------|------------|------------|------------|------------|--------------------|
| Distribution of lactose concentrations—mg. per 100 cc.           |             |         |          |          |          |          |          |          |            |            |            |            |            |                    |
| Group                                                            | Total Cases | 0 to 4  | 5 to 9   | 10 to 14 | 15 to 19 | 20 to 29 | 30 to 39 | 40 to 49 | 50 to 59   | 60 to 69   | 100 to 199 | 200 to 299 | 300 to 399 | Average Lactose    |
| Control                                                          | no. 24      | no. 18  | no. 3    | no. 3    | no. 0    | no. 6    | no. 0    | no. 0    | no. 0      | no. 0      | no. 0      | no. 0      | no. 0      | mg/100 cc. 2.5     |
| Lactating                                                        | 11          | 0       | 1        | 1        | 0        | 1        | 0        | 0        | 1          | 1          | 2          | 2          | 0          | 148.0              |
| Pregnant                                                         | 42          | 6       | 6        | 7        | 2        | 7        | 7        | 3        | 2          | 2          | 0          | 0          | 0          | 23.0               |
| Other (non-lactose) fermentable sugar—largely or wholly glucose. |             |         |          |          |          |          |          |          |            |            |            |            |            |                    |
| Distribution of glucose concentrations—mg. per 100 cc.           |             |         |          |          |          |          |          |          |            |            |            |            |            |                    |
| Group                                                            | Total Cases | 0 to 4  | 5 to 9   | 10 to 14 | 15 to 19 | 20 to 29 | 30 to 39 | 40 to 49 | 50 to 59   | 60 to 69   | 100 to 199 | 200 to 299 | 300 to 399 | Average Glucose    |
| Control                                                          | no. 24      | no. 5   | no. 5    | no. 5    | no. 1    | no. 3    | no. 2    | no. 1    | no. 0      | no. 1      | no. 1      | no. 0      | no. 0      | mg/100 cc. 19.8    |
| Lactating                                                        | 11          | 2       | 1        | 1        | 3        | 1        | 0        | 0        | 1          | 1          | 1          | 0          | 0          | 37.6               |
| Pregnant                                                         | 42          | 5       | 0        | 5        | 3        | 5        | 7        | 6        | 3          | 2          | 4          | 1          | 1          | 72.4               |
| Total fermentable sugar—glucose plus lactose.                    |             |         |          |          |          |          |          |          |            |            |            |            |            |                    |
| Distribution of sugar concentrations—mg. glucose per 100 cc.     |             |         |          |          |          |          |          |          |            |            |            |            |            |                    |
| Group                                                            | Total Cases | 0 to 24 | 25 to 29 | 30 to 39 | 40 to 49 | 50 to 59 | 60 to 69 | 70 to 79 | 100 to 199 | 200 to 299 | 300 to 399 | 500 to 599 | 900 to 999 | Average as Glucose |
| Control                                                          | no. 24      | no. 16  | no. 2    | no. 2    | no. 2    | no. 6    | no. 1    | no. 0    | no. 1      | no. 0      | no. 0      | no. 0      | no. 0      | mg/100 cc. 22      |
| Lactating                                                        | 11          | 2       | 0        | 1        | 0        | 0        | 1        | 2        | 1          | 2          | 2          | 0          | 0          | 155                |
| Pregnant                                                         | 42          | 6       | 4        | 2        | 7        | 7        | 5        | 4        | 5          | 0          | 0          | 1          | 1          | 91                 |

could be determined when the urine was not diluted before analysis. When dilute solutions of urine were studied, the method was applicable to very large amounts of lactose. In carrying out the procedure, control tubes containing lactose added to urine to give concentrations of 20 mg. per 100 cc. were routinely inoculated, incubated, and analyzed. The average recovery in 21 experiments of this sort was 99 per cent.

#### CLINICAL DATA

The method was applied to the study of urine specimens voided between 10 and 11 o'clock by women who, in the most instances, had eaten breakfast. Pregnant women, lactating women, and a control series of women between the ages of 18 and 45 from the wards and Out Patient Department of the Buffalo General Hospital were included. The specimens of urine from pregnant and lactating women were obtained from cases on the service of Dr. F. C. Goldsborough. As a part of the investigation, 290 specimens of urine from pregnant women on this service were tested with Benedict's qualitative reagent. Sixty-eight, or 23.4 per cent, of these gave a reaction interpreted as positive. Snoeck (3), in a similar series, found that only between 3 and 5 per cent gave positive reactions. It seems probable that slight differences in technique and in the interpretation of results explain the difference between the figures. Fifty-four per cent of 90 urine specimens obtained from women after delivery gave positive reactions. Of the control series, selected because the age and sex made them fairly comparable with the others, 12 per cent gave positive reactions with Benedict's solution. In Table I the results of the quantitative studies made are presented.

#### DISCUSSION

The results given in Table I can conveniently be grouped for discussion according to the three types of cases studied. The series used as a control seems to be unique, for no other attempt at quantitating the lactose in the urine of women who were neither pregnant nor lactating was found in the survey of the literature made.

Twenty-four women were studied. Eighteen of these gave results which were negative—which at least were lower than was the concentration determined by our method—but three specimens contained definite traces of lactose (Foot-note 3). The highest concentration found was 13 mg. per 100 cc. of urine. It seems probable that these traces were of alimentary origin, since there is evidence available in the work of Winter (4), Watkins (21) and of Snoeck (3) that lactosuria can arise in this way.

Practically every one of the control urines contained some sugar which was fermented by both the organisms used. It seems almost certain that this sugar was glucose. The amounts were of the order of magnitude which have been almost regularly found in samples of urine obtained from normal subjects after meals.

*Lactating women:* The findings on lactating women were similar to those of other investigators (Watkins (21), Winter (4), Willway (22), Kleiner and Tauber (8), Nizza (23), Castellani (10), and Amalfitano and

Roberto (24) who have studied this problem. Lactose was undoubtedly present in 11 of the 12 specimens analyzed (92 per cent), and the remaining specimen apparently contained 9 mg. per cent of lactose, a value which we have decided to include in the questionable range (Foot-note 3). The percentage of positive values is higher than that reported by some previous observers; this probably results from the great delicacy of the method which we used.

This series, which was carried out primarily as a control upon the studies of pregnant women, is too small to serve as a basis for an extended study of variations in the degree of lactosuria in different stages of lactation. Table II has nevertheless been prepared, and is given because it demonstrates that

TABLE II  
*Concentration of sugar in urine after parturition*

| Day After Parturition | Number of Cases | Series Number | Reaction with Benedict Qualitative Reagent | Lactose mg 100 cc. | Glucose mg 100 cc. |
|-----------------------|-----------------|---------------|--------------------------------------------|--------------------|--------------------|
| 1st                   | 1               | 1A            | —                                          | 29                 | 11                 |
| 2nd                   | 0               | —             | —                                          | —                  | —                  |
| 3rd                   | 1               | 3A            | ++                                         | 330                | 55                 |
| 4th                   | 0               | —             | —                                          | —                  | —                  |
| 5th                   | 2               | 5A<br>5B      | ++<br>++                                   | 105<br>245         | 4<br>195           |
| 6th                   | 0               | —             | —                                          | —                  | —                  |
| 7th                   | 1               | 7A            | ++                                         | 205                | 16                 |
| 8th                   | 0               | —             | —                                          | —                  | —                  |
| 9th                   | 1               | 9A            | ++                                         | 220                | 65                 |
| 10th                  | 2               | 10A<br>10B    | ++<br>++                                   | 155<br>78          | 24<br>15           |
| 11th                  | 2               | 11A<br>11B    | —<br>—                                     | 9<br>14            | 0<br>6             |
| 4 months              | 1               | X             | ++                                         | 57                 | 18                 |

our results were in approximate agreement with those of earlier observers. For example, Watkins (21) and Nizza (23) both found that urinary lactose was low during the first few days after parturition, rose to a peak on the third to the fifth day as the breasts filled with milk, and then gradually declined. It is clear that the results in Table II show similar relationships. The generally accepted explanation of these changes, which seems to be an adequate one, is that stagnation in the breasts occurs during the early days of the puerperium and an absorption of lactose into the blood stream is produced. As the infant begins to nurse regularly and the breasts are practically completely emptied, the lactose overflow is greatly diminished. As shown in Table II, a single analysis was carried out on the urine of a woman who was nursing her child 4 months after delivery. A fairly high concentration of lactose (57 mg. per 100 cc.) was found. Lactosuria may, therefore, persist in some instances for a fairly long period of time after delivery and the urine may contain enough lactose to give a positive reaction with Benedict's reagent, as it did in this instance.

The figures upon the glucose content of the urines from pregnant women are also interesting. It has been stated that sugars other than lactose are absent from the urine of lactating women who show lactosuria. This was not the case in the series presented. The average glucose content was greater in the lactating than in the control group. It seems doubtful whether much emphasis should be laid upon this difference between these averages for a number of reasons. The series was too small to serve as a basis for valid comparisons; the urines of the lactating women con-

(3) In interpreting the clinical data, a figure of 10 mg. per 100 cc. has been arbitrarily chosen as the lowest value showing the presence of a definite amount of lactose. As already stated, results as low as 5 mg. per 100 cc. appear to be significant, but it has seemed better to adopt the more conservative figure for this discussion.



tained such large amounts of sugar that it was necessary to dilute them before carrying out the analysis (Foot-note 2) and the figures for glucose were obtained in most instances by multiplying small determined values by 5; and, thirdly, except for two or three results, the amounts were almost the same in the lactating and control series.

It appears most probable, but not absolutely certain, that lactating women usually excrete approximately the same amounts of sugars other than lactose as do normal women of the same age group. If this is true, it seems improbable that galactose, the sugar from which lactose is in part derived, is present in the urine in any considerable quantity, as this sugar would be determined together with glucose by the method used.

*Pregnant women:* The present investigation was

There seem to be four or five possible explanations for the presence of lactose in the urine of pregnant women. (1) The sugar may be alimentary in origin. The Authors, as already stated, believe that the occasional presence of traces of lactose in the urine of normal women probably can be explained in this way. The low incidence of lactosuria in the control series compared with the relatively large number of positive findings in the pregnancy group seems to exclude such an explanation for the lactosuria of pregnancy. (2) The renal threshold for lactose may be low in pregnancy. If such a condition were present, ingested lactose might be excreted easily by pregnant women, and the results be adequately explained. The frequency with which non-diabetic glycosuria occurs in pregnancy, which has been often discussed, and which is illustrated by the results obtained in this study, might

TABLE III  
*Sugars excreted in different months of pregnancy*

| Month | Total Cases | Distribution of lactose concentrations—mg. per 100 cc. |        |          |          |          |          |          |          |          |             | Average lactose | Average glucose |
|-------|-------------|--------------------------------------------------------|--------|----------|----------|----------|----------|----------|----------|----------|-------------|-----------------|-----------------|
|       |             | 0 to 4                                                 | 5 to 9 | 10 to 14 | 15 to 19 | 20 to 29 | 30 to 39 | 40 to 49 | 50 to 59 | 60 to 80 |             |                 |                 |
|       |             | No.                                                    | No.    | No.      | No.      | No.      | No.      | No.      | No.      | No.      |             |                 |                 |
| 10th  | 12          | 1                                                      | 3      | 1        | 0        | 2        | 4        | 0        | 1        | 0        | mg. 100 cc. | mg./100 cc.     |                 |
| 9th   | 10          | 2                                                      | 0      | 2        | 0        | 1        | 2        | 2        | 0        | 1        | 22.2        | 105.9           |                 |
| 8th   | 9           | 1                                                      | 1      | 1        | 2        | 1        | 0        | 1        | 1        | 1        | 27.6        | 44.0            |                 |
| 7th   | 2           | 0                                                      | 1      | 1        | 0        | 0        | 0        | 0        | 0        | 0        | 29.5        | 84.6            |                 |
| 6th   | 2           | 0                                                      | 0      | 0        | 0        | 1        | 1        | 0        | 0        | 0        | 9.0         | 44.5            |                 |
| 5th   | 2           | 0                                                      | 0      | 1        | 0        | 1        | 0        | 0        | 0        | 0        | 27.5        | 77.5            |                 |
| 4th   | 2           | 1                                                      | 0      | 1        | 0        | 0        | 0        | 0        | 0        | 0        | 17.5        | 25.0            |                 |
| 3rd   | 1           | 0                                                      | 0      | 0        | 0        | 1        | 0        | 0        | 0        | 0        | 9.0         | 90.0            |                 |
| ?     | 2           | 1                                                      | 1      | 0        | 0        | 0        | 0        | 0        | 0        | 0        | 25.0        | 10.0            |                 |
|       |             |                                                        |        |          |          |          |          |          |          |          | 5.0         | 42.5            |                 |

directed primarily to the study of pregnant women, and the results upon them deserve especial emphasis. Thirty urines, or 71 per cent of the number analyzed, contained significant traces of lactose. Grandhomme (25), and Commandeur and Porcher (26) reported similar findings, but the incidence is much higher than that reported in many papers. It seems probable that this high incidence is due to the delicacy of the method of analysis used; in fact Snoeck (3), (who found that during the whole period of pregnancy 1 per cent of the cases showed lactosuria, and that during the last months a maximum of 7 per cent gave this finding), stated explicitly that higher figures would probably be found when better technical methods were available.

As will be seen in Table III, the averages of the lactose concentrations in the different months was practically constant throughout pregnancy. It is probable that great emphasis should not be placed upon this constancy because the number of urine specimens obtained during the early months was rather small. It is certain, however, as has been reported also by some previous observers, that lactosuria is not infrequent during the early months of pregnancy. The Table also shows that the greatest concentrations of lactose occurred during the latter months, but that negative values were not infrequently found at that time. These results are also in accord with series which have been reported previously. It seems to the Authors especially interesting that negative findings were encountered as late as the tenth month; the negative findings reported previously have frequently meant only that less than 0.05 per cent was present—the lowest amount demonstrated by many of the methods used.

be a point in favor of such an hypothesis, for if the threshold is low for one sugar, it is not difficult to believe that it is low for another also. The Authors do not believe, however, that there is a low threshold for lactose during pregnancy, partly because there was no relationship between the degrees of glycosuria and of lactosuria in the different cases studied, and partly because the renal threshold for lactose is always so low as to be practically zero. A number of blood samples from normal, lactating, and pregnant women were analyzed by a method, to be described in detail later, which will demonstrate lactose in concentrations as low as 1 mg. per 100 cc. of plasma. Negative results were regularly obtained except in blood from a very few lactating women who were excreting large amounts of lactose. The maximum concentration found was 2 mg. per 100 cc. of plasma. (3) A third possibility is that liver damage, which some observers (27, 28, 29) believe exists during pregnancy, may lead to the excretion of lactose as it sometimes does to the excretion of levulose and galactose. This explanation seems improbable for two reasons: (A) Impaired levulose tolerance is not readily demonstrated in normal pregnancy (30), and (B) lactose is practically wholly split in the digestive tract, and very little unaltered disaccharide reaches the liver. If a decreased liver function plays any part in the lactosuria of pregnancy, it is almost necessary to assume also that an unusual amount of unaltered sugar is reaching the liver, either by absorption through the wall of the gut, or from some other source. (4) The fourth possibility is that pregnant women excrete lactose because small amounts of sugar are formed in the mammary glands, which are developing some de-

gree of activity, and that this sugar escapes into the blood stream and urine.

To the Authors the last theory appears to be the most probable one. Their reasons are: (A) that the other explanations offered above seem to them to be inadequate; (B) that our theory accounts adequately for the high incidence of positive findings (71 per cent of all specimens gave results which were certainly positive); (C) that it explains lactosuria in the presence of very low concentrations of lactose in the blood; and, (D) that it seems to the Authors to account adequately for the occurrence of positive results throughout pregnancy and also the presence of the highest concentrations just before parturition. (5) A fifth possible explanation should also be mentioned. Possibly unaltered lactose may pass through the in-

In Tables IV and V the specimens upon which positive and negative reactions with Benedict's qualitative reagent were obtained have been given separately. Specimens with reactions recorded as  $\pm$  are classified with those more strongly positive. For convenience both sugars were expressed as glucose in computing the data. Inspection of these Tables shows that, in our hands, results of this test corresponded quite closely with definite concentrations of total fermentable sugar in urine. All specimens containing more than 60 mg. per cent gave positive reactions, while all but two containing less than 40 mg. gave negative ones. In the two exceptions, which were both urines from pregnant women, it was quite clear that the result was largely due to the unusual amount of non-

TABLE IV

*Concentrations of sugar in urine giving positive reactions with Benedict's reagent*

| Lactose.                                                                    |             |                                                              |          |          |          |          |          |          |            |            |            |            |            |                    |
|-----------------------------------------------------------------------------|-------------|--------------------------------------------------------------|----------|----------|----------|----------|----------|----------|------------|------------|------------|------------|------------|--------------------|
| Group                                                                       | Total Cases | Distribution of lactose concentrations—mg. per 100 cc.       |          |          |          |          |          |          |            |            |            |            |            | Average Lactose    |
|                                                                             |             | 0 to 4                                                       | 5 to 9   | 10 to 14 | 15 to 19 | 20 to 29 | 30 to 39 | 40 to 49 | 50 to 59   | 60 to 99   | 100 to 199 | 200 to 299 | 300 to 399 |                    |
| Control                                                                     | no. 3       | no. 2                                                        | no. 1    | no. 0    | no. 0    | no. 0    | no. 0    | no. 0    | no. 0      | no. 0      | no. 0      | no. 0      | no. 0      | mg./100 cc. 1.6    |
| Lactating                                                                   | S 0         | 0                                                            | 0        | 0        | 0        | 0        | 0        | 0        | 1          | 1          | 2          | 2          | 2          | 73.3               |
| Pregnant                                                                    | 25          | 2                                                            | 3        | 4        | 2        | 3        | 5        | 2        | 2          | 2          | 0          | 0          | 0          | 48.8               |
|                                                                             |             |                                                              |          |          |          |          |          |          |            |            |            |            |            | 111.0              |
| Other (non-lactose) fermentable sugars—largely or wholly glucose.           |             |                                                              |          |          |          |          |          |          |            |            |            |            |            |                    |
| Group                                                                       | Total Cases | Distribution of glucose concentrations—mg. per 100 cc.       |          |          |          |          |          |          |            |            |            |            |            | Average Glucose    |
|                                                                             |             | 0 to 4                                                       | 5 to 9   | 10 to 14 | 15 to 19 | 20 to 29 | 30 to 39 | 40 to 49 | 50 to 59   | 60 to 99   | 100 to 199 | 200 to 299 | 300 to 399 |                    |
| Control                                                                     | no. 3       | no. 0                                                        | no. 0    | no. 0    | no. 0    | no. 0    | no. 0    | no. 1    | no. 0      | no. 1      | no. 1      | no. 0      | no. 0      | mg./100 cc. 73.3   |
| Lactating                                                                   | S 1         | 1                                                            | 0        | 0        | 3        | 1        | 0        | 0        | 1          | 1          | 1          | 0          | 0          | 48.8               |
| Pregnant                                                                    | 25          | 1                                                            | 0        | 1        | 0        | 2        | 6        | 4        | 3          | 2          | 4          | 1          | 1          | 111.0              |
| Total fermentable sugar—glucose plus lactose.                               |             |                                                              |          |          |          |          |          |          |            |            |            |            |            |                    |
| Group                                                                       | Total       | Distribution of sugar concentrations—mg. glucose per 100 cc. |          |          |          |          |          |          |            |            |            |            |            | Average as Glucose |
|                                                                             |             | 0 to 24                                                      | 25 to 29 | 30 to 39 | 40 to 49 | 50 to 59 | 60 to 69 | 70 to 99 | 100 to 199 | 200 to 299 | 300 to 399 | 500 to 599 | 900 to 999 |                    |
| Control                                                                     | no. 3       | no. 0                                                        | no. 0    | no. 0    | no. 1    | no. 0    | no. 1    | no. 0    | no. 1      | no. 0      | no. 0      | no. 0      | no. 0      | mg./100 cc. 75     |
| Lactating                                                                   | S 0         | 0                                                            | 0        | 0        | 0        | 0        | 0        | 2        | 1          | 2          | 2          | 0          | 0          | 205                |
| Pregnant                                                                    | 25          | 0                                                            | 1*       | 1**      | 3        | 4        | 5        | 4        | 5          | 0          | 0          | 1          | 1          | 131                |
| Non-sugar reducing compounds (*) 79. (**) 67 mg. glucose per 100 cc. urine. |             |                                                              |          |          |          |          |          |          |            |            |            |            |            |                    |

testinal wall more easily in pregnancy than it does under normal conditions. While this explanation is possibly correct, it appears to the Authors that it is not so probable as is the one based upon activity of the mammary glands which has been discussed above.

It will be seen from Table I that most pregnant women excreted sugar which was not lactose. The average of the figures and the incidence of high values were both markedly higher in this group than they were in the lactating or control group. It seems almost certain that this sugar was glucose, although the presence of galactose cannot be excluded. It has long been thought that a benign glycosuria due to glucose occurs frequently during pregnancy. Results obtained conform to this belief, for blood sugar determinations were carried out on those patients who showed marked glycosuria, and normal values found in samples taken after a night's fast.

sugar reducing compounds which they contained, for in both, the concentration of such compounds was well above 50.5 mg. per 100 cc., the average of the results in the whole series. As far as could be made out, these two specimens were the only ones in which the amounts of non-sugar reducing compounds affected the reaction with Benedict's solution; results upon all other specimens could be adequately explained by the amounts of sugar which they contained.

It seems worth while to inquire into the part played by glucose and lactose in causing positive reactions in the three different groups of patients studied. The three positive tests in the control series were all due to glucose, for each specimen contained more than 40 mg. of that sugar per 100 cc. Each of the positive tests in the lactating women adequately could be explained by the amount of lactose which was present,



for in every instance this was more than 40 mg. per 100 cc. (expressed in terms of its glucose equivalent, i.e. lactose divided by 1.24).

It is somewhat more difficult to decide what sugar was responsible for the positive finding in some of the specimens from pregnant women. As has already been pointed out, an increased concentration of both glucose and lactose was present in many instances. Glucose alone might have caused a positive test more often than lactose, for 15 specimens, or three-fifths of those giving positive results, contained more than 40 mg. of glucose per 100 cc., while a similar concentration of lactose (expressed as its glucose equivalent) was present in only four of them. In six of the specimens neither sugar was present in amounts sufficiently great to give positive tests, but the sum of the two exceeded

first days after parturition. It can be demonstrated, at least in some instances, months after delivery. The lactosuria probably results from an overflow of active mammary glands.

(4) Lactose is present in small amounts in the urine of a large proportion of pregnant women. Sometimes it can be demonstrated in the early months of pregnancy, but is not always found, even in the days immediately preceding parturition. In the opinion of the Authors this lactosuria is caused by activity of the mammary glands.

(5) Glucose (fermentable sugar which is not lactose) was present in the urine of our series of lactating women in slightly greater concentration than it was in the urine of a comparable series of non-pregnant, non-lactating women, but the difference was

TABLE V  
Concentrations of sugar in urine giving negative reactions with Benedict's reagent

| Lactose.                                                          |             |                                                              |          |          |          |          |          |          |            |            |            |            |            |                    |
|-------------------------------------------------------------------|-------------|--------------------------------------------------------------|----------|----------|----------|----------|----------|----------|------------|------------|------------|------------|------------|--------------------|
| Group                                                             | Total Cases | Distribution of lactose concentrations—mg. per 100 cc.       |          |          |          |          |          |          |            |            |            |            |            | Average Lactose    |
|                                                                   |             | 0 to 4                                                       | 5 to 9   | 10 to 14 | 15 to 19 | 20 to 29 | 30 to 39 | 40 to 49 | 50 to 59   | 60 to 99   | 100 to 199 | 200 to 299 | 300 to 399 |                    |
| Control                                                           | no. 21      | no. 16                                                       | no. 2    | no. 3    | no. 0    | no. 0    | no. 0    | no. 0    | no. 0      | no. 0      | no. 0      | no. 0      | no. 0      | mg/100 cc. 2.6     |
| Lactating                                                         | 3           | 0                                                            | 1        | 1        | 0        | 1        | 0        | 0        | 0          | 0          | 0          | 0          | 0          | 17.3               |
| Pregnant                                                          | 17          | 4                                                            | 3        | 3        | 0        | 4        | 2        | 1        | 0          | 0          | 0          | 0          | 0          | 16.3               |
| Other (non-lactose) fermentable sugars—largely or wholly glucose. |             |                                                              |          |          |          |          |          |          |            |            |            |            |            |                    |
| Group                                                             | Total Cases | Distribution of glucose concentrations—mg. per 100 cc.       |          |          |          |          |          |          |            |            |            |            |            | Average Glucose    |
|                                                                   |             | 0 to 4                                                       | 5 to 9   | 10 to 14 | 15 to 19 | 20 to 29 | 30 to 39 | 40 to 49 | 50 to 59   | 60 to 99   | 100 to 199 | 200 to 299 | 300 to 399 |                    |
| Control                                                           | no. 21      | no. 5                                                        | no. 5    | no. 5    | no. 1    | no. 3    | no. 2    | no. 0    | no. 0      | no. 0      | no. 0      | no. 0      | no. 0      | mg/100 cc. 12.1    |
| Lactating                                                         | 3           | 1                                                            | 1        | 1        | 0        | 0        | 0        | 0        | 0          | 0          | 0          | 0          | 0          | 5.6                |
| Pregnant                                                          | 17          | 4                                                            | 0        | 4        | 3        | 3        | 1        | 2        | 0          | 0          | 0          | 0          | 0          | 17.5               |
| Total fermentable sugar—glucose plus lactose.                     |             |                                                              |          |          |          |          |          |          |            |            |            |            |            |                    |
| Group                                                             | Total       | Distribution of sugar concentrations—mg. glucose per 100 cc. |          |          |          |          |          |          |            |            |            |            |            | Average as Glucose |
|                                                                   |             | 0 to 24                                                      | 25 to 29 | 30 to 39 | 40 to 49 | 50 to 59 | 60 to 69 | 70 to 99 | 100 to 199 | 200 to 299 | 300 to 399 | 500 to 599 | 900 to 999 |                    |
| Control                                                           | no. 21      | no. 16                                                       | no. 2    | no. 2    | no. 1    | no. 0    | no. 0    | no. 0    | no. 0      | no. 0      | no. 0      | no. 0      | no. 0      | mg/100 cc. 14      |
| Lactating                                                         | 3           | 2                                                            | 0        | 1        | 0        | 0        | 0        | 0        | 0          | 0          | 0          | 0          | 0          | 19                 |
| Pregnant                                                          | 17          | 6                                                            | 3        | 1        | 4        | 3        | 0        | 0        | 0          | 0          | 0          | 0          | 0          | 30                 |

40 mg. per 100 cc., while in two, as already mentioned, the non-sugar reducing compounds appeared to determine the type of copper reduction test obtained. Arguing from these results, a positive test with Benedict's reagent in urine from a case of pregnancy means that glucose is probably present in amounts greater than the slight traces contained in most normal urines.

### CONCLUSIONS

- (1) A specific sensitive method for quantitatively estimating lactose in urine is described.
- (2) Lactose is usually absent from the urine of normal women, although occasionally traces, probably of alimentary origin, may be found.
- (3) Lactose is almost always present in increased amounts in the urine of lactating women during the

small and probably not significant. Sugar of this type was present in quite large amounts in the urine of pregnant women. In our series this glycosuria did not appear to be clinically significant.

(6) Positive reactions with Benedict's qualitative reagent were due to glucose in the urine from normal subjects, to lactose in the urine from lactating women, and in a majority of instances to glucose in the urine of pregnant women.

### ACKNOWLEDGMENT

Our thanks are due to Dr. F. C. Goldsborough and the staff of the obstetrical service for aid in obtaining the urines from pregnant and lactating women, and to Dr. Stuart L. Vaughan for help in carrying out the bacteriological work involved in developing the method described.

### REFERENCES

1. Blot: De la glycosurie physiologique des femmes en couches, des nourrices et d'un certain nombre de femmes enceintes, *Gazette hebdomadaire*, p. 720, 1856, through Snoeck (3).
2. Hofmeister, F.: Ueber Lactosurie, *Ztschr. f. Physiol. Chem.*, 1:101-110, 1877.
3. Snoeck, J. J.: Recherches sur la glycosurie et la lactosurie gravidique, *Arch. Internat. de Méd. Expér.*, 7:349-418, Aug., 1932.
4. Winter, L. B.: The metabolism of lactose, *J. Physiol.*, 71:341-355, Apr., 1931.

5. Winter, L. B.: The metabolism of lactose: blood sugar during lactation, *J. Physiol.*, 77:100-103, Dec., 1932.
6. Kownski, A.: Zur Methodik der Milchezuckerbestimmung im Blute, *Ztschr. f. Klin. Med.*, 102:382-387, June, 1925.
7. Gootz, R., and Tunger, H.: Lactosenachweis im Harn, *Ztschr. F. Physiol. Chem.*, 217:28-32, Mar., 1933.
8. Kleiner, I. S., and Tauber, H.: Practical method for simultaneous estimation of lactose and glucose in the urine, *J. Biol. Chem.*, 100:749-751, May, 1933.
9. Castellani, A.: Detection of saccharosuria, inosituria und lactosuria by mycological method, *Brit. M. J.*, 1:183, Feb., 1919.
10. Castellani, A.: Brief note on lactosuria in nursing women, *J. Trop. Med.*, 31:213-214, Sept., 1928.
11. Castellani, A.: Lactosuria in nursing women: its detection by simplified bacterial method, *J. A. M. A.*, 90:1773-1774, June, 1928.
12. Standring, T.: Detection of lactosurin by bacterial method of Castellani and Taylor, *J. Trop. Med.*, 35:373-377, Dec., 1932.
13. Harding, V. J., and Selby, D. L.: Fermentable sugar in normal urine, *Biochem. J.*, 25:1815-1838, 1931.
14. Harding, V. J., Nicholson, T. F., Grant, G. A., Hern, G., and Downs, C. E.: Preliminary account of analytical methods for individual carbohydrates, *Trans. Roy. Soc. of Can.*, 26:33-33, 1932.
15. Harding, V. J., and Nicholson, T. F.: The use of some micro-organisms in sugar analysis, *Biochem. J.*, 27:1082-1084, 1933.
16. Harding, V. J., and Selby, D. L.: Fermentable sugar in fasting urine, *Biochem. J.*, 27:1598-1608, 1933.
17. Hubbard, R. S., and Kingsbury, M.: The bacterial determination of lactose in blood, *Proc. Soc. Exp. Biol. and Med.*, 28:93-94, 1930.
18. Folia, O., and Wu, H.: A system of blood analysis. A simplified and improved method for determination of sugar, *J. Biol. Chem.*, 41:367, Mar., 1920.
19. Sumner, J. B., and Noback, C. V.: Estimation of sugar in diabetic urine using dinitrosalicylic acid, *J. Biol. Chem.*, 62:287-290, Dec., 1924.
20. Sumner, J. B., and Graham, V. A.: Dinitrosalicylic acid: a reagent for estimation of sugar in normal and diabetic urine, *J. Biol. Chem.*, 47:5, June, 1921.
21. Watkins, O.: Lactose metabolism in women, *J. Biol. Chem.*, 80:33-66, Nov., 1928.
22. Willway, F. W.: Detection of lactose in the urine by the Castellani-Taylor mycological method, *J. Trop. Med.*, 34:133-134, May, 1931.
23. Nizza, M.: Nota intorno alla lattosuria in gravidanza e in puerperio. Ricerche col metodo micologico Castellani-Taylor, *Rassegna d'ostet e ginec.*, 40:664-670, Oct., 1931.
24. Amalfitano, G., and Roberto, S.: La lattosuria e il metodo micologico di Castellani-Taylor per svelarla, *Policlinico (sez. prat.)*, 39:1451-1465, Sept., 1932.
25. Grandhomme, H.: Contribution à l'étude de l'élimination des sucres urinaires chez la femme enceinte, *Thèse de Paris*, 1923.
26. Commandeur and Porcher, C.: Recherches sur les sucres urinaires chez la femme enceinte, en couches et nourrice, *Arch. Gén. de Méd.*, 2:2241-2264 and 2305-2323, 1904.
27. Soffer, L. J.: Bilirubin excretion as a test for liver function during normal pregnancy, *Bull. Johns Hopkins Hosp.*, 52:356-375, May, 1933.
28. Hofbauer, J.: Organveränderungen während der Gravidität und ihre biologische Bedeutung, *Monatschr. f. Geburt u. Gynäk.*, 25:743, 1907.
29. Seitz, L.: Die Schwangerschaftsveränderung im Lichte der modernen Forschung und in ihrem Zusammenhang mit den Schwangerschaftstoxikosen, *Monatschr. f. Geburt u. Gynäk.*, 75:323, Jan., 1927; *Med. Klinik*, 23:1401, Sept., 1927.
30. Cross, R. S.: A study of various liver function tests in normal pregnancy, *Am. J. of Obst. and Gynec.*, 18:800-807, Dec., 1929.

## Dry Natural Digestive Juices: Their Properties and Laboratory and Clinical Use<sup>\*</sup>

By

W. N. BOLDYREFF, M.D.

BATTLE CREEK, MICHIGAN

**W** BEAUMONT was the pioneer in the study of the natural digestive juices, but it was I. P. Pavlov who made a more complete investigation. It is quite evident that the natural juices cannot be substituted by any artificial products since such preparations do not contain all the component parts of the natural juices and are besides rendered impure by various admixtures. All this may lead to serious errors, if one assumes the data obtained from artificial juices to be true of the live juices. An outstanding example of this is the assertion that the gastric juice contains lipase. Now, some of the natural digestive juices are widely used not only in every day laboratory work but for instance, gastric juice is introduced into the clinic as medicine. Moreover, during the World war an attempt was made to use gastric juice as an antiseptic for old used bandages, to clean them of pus; (Professor Leontovich, Moscow<sup>\*\*</sup>). However, the fact that digestive juices in their natural state are highly watery and they do not keep well, prevented their wide application. In the gastric juice and saliva, water content may exceed 99½ per cent. Therefore in storage and mailing, the natural digestive juices occupy much extra space, require large fragile packing vessels, adding as much weight as the juices themselves. The natural pancreatic juice, especially in its

active state is so easily decomposed due to autodigestion and presence of microbes that it can be preserved only in the frozen state which is very difficult to achieve if it is to be stored for a long period or intended for transportation. All these complications are easily avoided when one uses all the named juices in a dried state. I mean the natural dry digestive juices and not the artificial preparations, such as dry pepsin, rennin and pancreatin. These artificial substances in their present state cannot completely substitute for the liquid natural living juices any more than anything could substitute for fresh milk or egg.

The natural digestive juices, fresh and pure, are to be found in many physiological laboratories. But it is difficult to store them, they require a lot of space and vessels, are quickly spoiled, and therefore are usually thrown away after being examined or even before, when time is short. Biochemical and other laboratories and clinics not unfrequently need such juices, but they cannot always have them, for, as a matter of fact, they do not know how to obtain them from the animals. E. Fischer (Berlin) some twenty-five years ago, used to order intestinal juice from Professor I. P. Pavlov's Laboratory in Petrograd. The German scientists decided that they ought to learn to meet their own scientific needs, and sent the young doctor Nikolai (now Professor in South America) to study with I. P. Pavlov.

<sup>\*</sup>Reported March 29, 1934, at the Annual Meeting of the American Physiological Society at Columbia University, New York, N. Y. Submitted January 1, 1935.

<sup>\*\*</sup>Natural active pancreatic juice or duodenal content could do this much better and quicker.

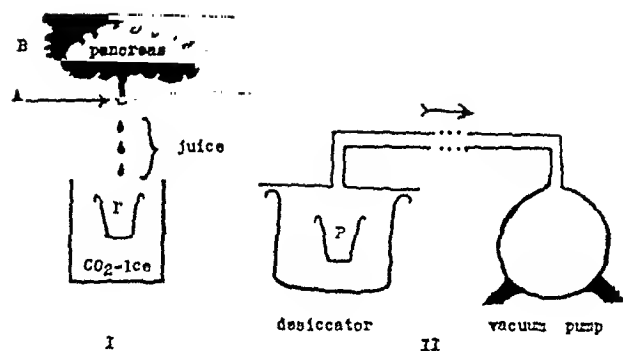


Fig. 1. PREPARATION OF DRY PANCREATIC JUICE. I—Obtaining juice from a fistular animal. B—portion of the animal's body. A—orifice of the pancreatic fistula. The pancreatic juice flows out into a receptacle, cooled by CO<sub>2</sub>-ice, in which it immediately freezes (P). Instead of freezing and drying the juice, it could be dropped directly into some alcohol. Then the ferments would settle down in white dregs. II—Drying the frozen pancreatic juice at 0°C and 0 pressure. The juice (P) is placed into the desiccator from which the air and water vapors are pumped out with a powerful vacuum pump.

In the summer of 1907 Dr. J. H. Kellogg visited I. P. Pavlov's Laboratory in Petrograd and borrowed 20 bottles of natural gastric juice to take home to the American physicians. But during the trip the juice moulded in all 20 bottles (mould is resistant to acids) and upon his return when he found that, he had to throw it away. Nothing of the kind would happen, if the juice were in the dried state.

Quite recently Dr. P. A. Levene of this country, went over to I. P. Pavlov, too, when he needed some intestinal and pancreatic juices; it was a very complicated and almost impossible matter to obtain them from Petrograd; then Dr. Levene asked me, and for some three years I supplied him with both the intestinal and the pancreatic juice, sending them to him in frozen state in a thermos bottle. Later I rendered the same service to Dr. J. H. Northrop of the Rockefeller Institute. Other similar services I have rendered many times in Russia, Japan and this country. Requests often came unexpectedly and we had to operate on animals, if we did not have the necessary fistular dogs. All this caused many difficulties and delays in our work, and for those whom I supplied with these juices.

For this reason, as far back as thirty years ago, I tried to obtain dry preparations of gastric, pancreatic and intestinal juices, drying them with heating up to 30°-40°C in a vacuum apparatus of S. K. Dzershowski (1). However, this process had so weakened the gastric juice, due to autodigestion, that it became practically inefficient, being much weaker than the commercial pepsin or rennin. And the pancreatic juice in this process was so deteriorated that it completely lost its digestive properties. But with the intestinal juice I solved this problem successfully in 1907; drying it at a temperature of 60°-80°C, I obtained a sufficient quantity of enterokynase which I used during the six years I worked at Kazan University where I have supplied with quantities of this preparation various physiologists and biochemists who needed it. My success with the intestinal juice depended on the fact that the enterokynase, as proven by Dr. N. P. Shepovallnikov in Pavlov's Laboratory, is not destroyed even in boiling for a short time. The dry intestinal juice proved to be very convenient and the quantity filling one ordinary test tube was more than enough to serve all my own, and other peoples' needs for six years, and its properties remained unchanged during all this time. A successful experiment with kynase has incited me to attempt preparations of all other digestive juice in the dry state. This winter I was at last successful in drying all digestive juices, using a vacuum pump and drying the juices in the frozen state according to Dr. L.

F. Shackell (2)\*. One can extract from the live digestive juices their active principle with alcohol or draw water from them with chemically pure glycerine (thrice crystallized), but these methods are less convenient and therefore I shall not describe them although I used both of them successfully. I tested these juices for ferments before and after drying and found that drying does not affect the ferments at all. The juices were tested in the following manner. For example, I was testing the saliva, the gastric juice or the pancreatic juice for ferments content, then a certain quantity of each juice was dried to a standard weight in frozen state. One must remember that dried juices like proteins in general are very hygroscopic. Having obtained a dried juice and knowing its weight, and the volume of liquid juice it corresponds to, it is a simple matter to calculate how much liquid it would require to restore the juice to its original condition before the drying. I added some distilled water to the dry saliva, pancreatic and other juice and some 0.5 per cent HCl to the dry gastric juice. Then I tested again all the restored juices for ferments content; the results of these tests showed that the quantity of all ferments in all of them remained unchanged. Thus, the problem of preparing all digestive juices and storing them for unlimited time can be considered as solved since we know that these substances being sterile do not change when properly stored in the dried state.

Experiments with storage of dried serums have long ago shown that they do not at all lose their medicinal properties during a number of years. A similar experiment proved to me, still earlier, that even the pancreatic juice, the least resistant and most easily destroyed, preserves unchanged its digestive properties practically for ever, if stored in frozen state and not allowed to thaw.

After the first tests described above I assigned myself three problems trying to establish exactly whether drying produces any changes whatever in the frozen juices. The first problem was to see whether the dried juice can afterwards be quickly and completely dissolved without residue, so that it would be perfectly restored to liquid state without any changes in its physico-chemical condition. The test gave positive results; all dried digestive juices can be dissolved without residue very quickly, in one minute or even sooner. The second problem: do such juices preserve their physiological properties intact, do they remain live and does not their ferment action weaken with drying? As mentioned above, tests for ferment content gave positive results. The third problem: does prolonged storage during months and years harmfully affect the properties of these juices, and if it does, how much,

\*This method was kindly recommended to me by Dr. L. H. Newburgh of Univ. of Michigan.

Fig. 2. STERILIZATION AND DRYING OF JUICES (without any dessicating substance). Diagram. a—sterile porcelain filter (marked by dotted line). b—sterile cotton. c—pet-cock.

and which ones? This question cannot be answered yet—it will require several years to test it out but study of the juices which were stored during several months gives us a hope that this problem can also be solved in the positive sense. It is quite probable that preparations of hilus, blood and other semiliquid substances of animal origin made in the described manner can be stored for an indefinite, unlimited time.

As for the laboratory use of dried, live or natural digestive juices, it is truly unlimited, may be of everyday application and is well known. For this reason there is no need for a detailed discussion of it at this time.

As for the clinical use of gastric juice, it is several scores of years ago that Professor I. P. Pavlov first introduced it into medical practice and other clinicians have warmly recommended it in Europe. In one of my early papers I discussed this in detail (3).

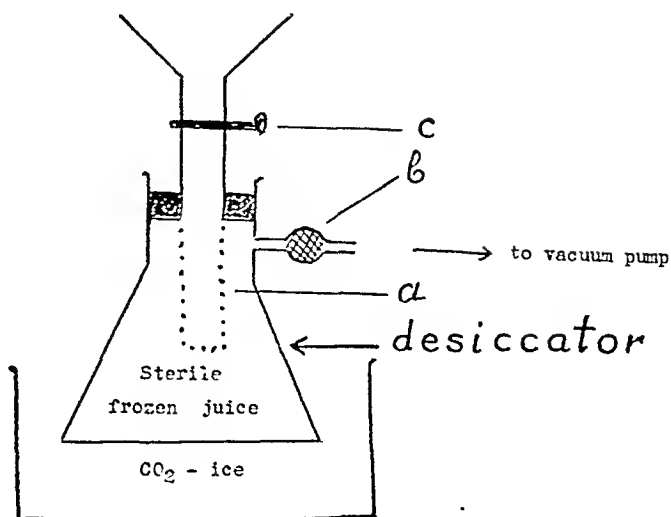
The clinical use of the gastric juice for treatment of digestive disorders has found a wide application in Russia, France, Germany, Sweden and other countries. I trust the method of preparing dry gastric juice may help to introduce it into the clinic and into medical use in general in this country. Professor Huchard of Paris has especially favored the gastric juice; he called it "digitalis for the digestive tract." Professor I. S. Zitovich in Russia used digestive juice as an aid in weakened digestion with great benefit in consumptive patients.

The pancreatic juice, I recommend for treatment of diabetes mellitus and hemophilia. The theoretical bases for this suggestion are found in my report to the XIVth International Physiological Congress in Rome in 1932 and in XIIth International Congress in Stockholm in 1926. Details of the practical application I will soon report to the meeting of the 37th American Gastroenterological Association and several medical societies. All this material will be published shortly. The dry bile and intestinal juice will be indispensable companions of the pancreatic juice being its activators and aids in digestion, and dry saliva probably will also find its clinical application in various cases of insufficient gastric digestion which can be improved by saliva, as we know.

I recommend to use dried hilus for extreme exhaustion and malnutrition, and in distinction from other juices, taken internally by mouth, hilus can be introduced subcutaneously and in extreme cases even directly into the blood stream.

Dried juices can be added to some foods, with great benefit, when prepared in the factories. The dry gastric and pancreatic juices are especially well suited for this, but other juices can be used too. The gastric juice is best added to proteins, and the pancreatic juice to proteins, carbohydrates and fats (for instance to dry milk, etc.). Such food stuffs would be very beneficial and convenient for anemic persons, for diabetic patients, and in certain other conditions.

The process of drying is the same for all digestive juices and it is very simple. (See Figures I and II). If necessary, they are first freed from microbes and other impurities through centrifugalization and filtra-



tion through a sterile porcelain filter; after this all work is done under sterile conditions; then the juices are frozen with the aid of dry ice ( $\text{CO}_2$ -ice). Working with the pancreatic juice, especially with the active pancreatic juice, one should not lose one minute: it spoils so quickly. The frozen juice is placed into the desiccator and dried by a powerful vacuum pump at  $0^\circ\text{C}$  and the atmospheric pressure at 0. If necessary, several pumps are placed in series, in line. Some drying substance ( $\text{H}_2\text{SO}_4$ ,  $\text{P}_2\text{O}_5$  or others which would not generate any gases, vapors or hard particles which may injure the juices) is placed into the dessicator, but one may dry without it too. When dried to a constant weight the dry juice is placed into a sterile vessel, if possible of dark glass, which is hermetically sealed and kept in a dark, dry, cool place.

In the end of this work I had kind assistance of Dr. W. B. Lewis who helped me to dry some digestive juices. In our joint paper we will describe in detail the process of drying such juices, as well as their physico-chemical properties as compared to the normal juices (specific gravity, reaction, pH, viscosity, etc.).

In case the juices are contaminated by some microbes during desiccation or afterwards, a remarkable change in their appearance takes place. Then instead of a powder of a light color the dry juice is turned into a sticky black jelly. We observed this change three times at the end of the drying various samples of gastric juice and once in already dried bile, which was spoiled in transportation, having been corked with an impure cork. The main supply of the bile, from which this portion was taken, remained unchanged a powder of a brownish color.

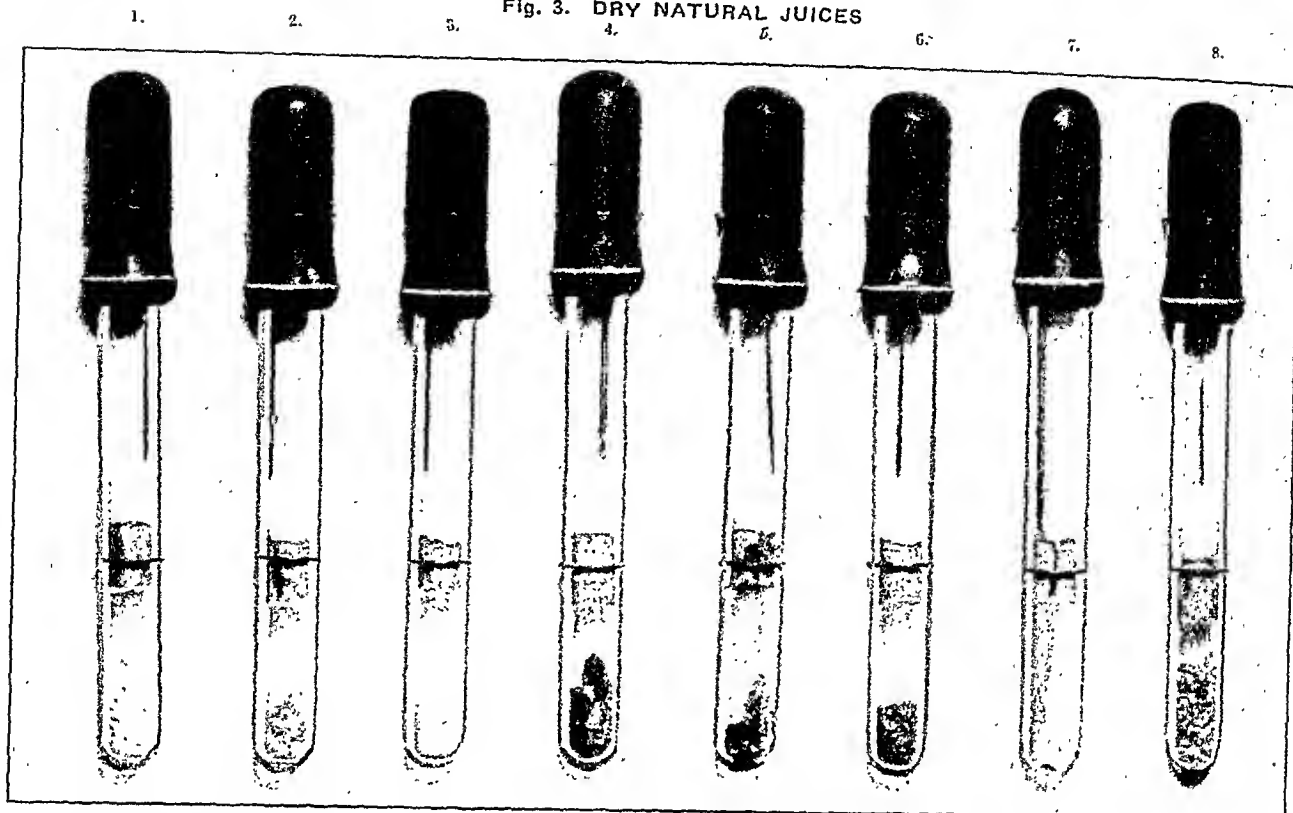
#### TECHNICAL

Any digestive juice freshly collected and cooled (not losing one minute) should be preserved in dry state without any antiseptic material. The juice is centrifugalized and if necessary filtered through a sterile porcelain filter directly into a sterile transparent\* glass vessel which is later placed into the dessicator cooled by  $\text{CO}_2$ -ice (dry ice), when necessary. The dessicator is best of a small size (not over 6 inches in diameter\*\*). When the juice cannot be dried immediately after collection, it must be saved in frozen state

\*In order to observe the process of drying.

\*\*Because a large one may be easily crushed by atmospheric pressure (Shackell).

Fig. 3. DRY NATURAL JUICES



only. With the aid of a powerful vacuum pump (pressure not exceeding 3 m. mercury), and temperature  $0^{\circ}$  Centigrade or lower, the juice is dried to a constant weight. When necessary, to hasten the process of drying some  $H_2SO_4$ ,

$P_2O_5$ , or other sterile desiccating substances, not generating harmful gaseous vapors or hard particles, capable or destroying the ferments of the juice, may be placed into the dessicator. The drying juice should be protected from such particles from above, since they may float like dust, when there is a sudden drop in pressure in the dessicator. The dry juice is immediately placed into a narrow sterile glass vessel, the opening of which is best soldered. The dry juice should be kept in a dark cool place, free from dust. (See Fig. VI, II and III).

#### SUMMARY

When drying in the described manner any digestive juice, its ferments are not in the least affected and lose none of their digestive properties. We tested saliva, gastric, pancreatic and intestinal juices, bile, duodenal content, and also prepared dry gastric and intestinal mucus. Our juices were mostly from dogs, sometimes from human subjects. Dry juices are very quickly, almost instantly, completely dissolved in water (gastric juice in 0.5 per cent HCl). In the dissolved state they are not distinguished from corresponding natural juices. When properly preserved in a dried state without change in their properties, the digestive juices may be kept for an indefinitely long time. Small quantities of dry juices, when not hermetically sealed, must be kept in the dessicator over  $H_2SO_4$ . The dry

1. Saliva, 2. Gastric Juice, 3. Gastric Mucus, 4. Duodenal Contents, 5. Bile, 6. Intestinal Juice, 7. Intestinal Mucus, 8. Pancreatic Juice. All canine with the exception of saliva and duodenal contents, which are human.

juices are very hygroscopic and easily contaminated by microbes.

#### CONCLUSIONS

1. Any digestive juice is collected, if possible aseptically and immediately frozen in a sterile vessel with the aid of some dry ice

( $CO_2$  in solid state).

2. The frozen juice is dried in a sterile dessicator with or without a desiccating substance to a constant weight without melting. In such state it can be preserved indefinitely, almost without losing its ferment properties and without spoilage.

3. Dried juices, as also proteins in general, quickly absorb moisture from the air and then become perishable; light may be destructive also, therefore they must be kept in hermetically sealed vessels in a dark room.

4. Insufficiently dried juices may spoil either due to self-digestion (especially active pancreatic juice) or to the effect of microbes; in the second case they grow dark in color and even black and turn into a gluey mass, and their ferment properties weaken or even totally disappear.

5. Sometimes this spoilage occurs during the process of drying (particularly if it has been long in non-sterile conditions or the juices thawed) and for that reason the process of drying must be very quick\*.

\*I do not know to how low a temperature one can subject the juices without losing their ferment action. Control experiments have shown that sometimes the temperature was  $40^{\circ}C$  below zero since mercury was frozen. Further experiments are necessary in order to determine the exact low temperature and duration of freezing period harmless for live juices. However, apparently, there is no ground to fear harmful effects from low temperature.

#### REFERENCES

1. Dzershgovski, S. K.: *Arch. des Sciences Biol.*, 1896. Petersburg.
2. Shackell, L. F.: *Am. Jour. of Physiol.*, 1909, Vol. 24, p. 325.
3. Boldyreff, W. N.: *Russky Vrach*, 1907, No. 5.

# ABSTRACTS

GOLDHAMER, S. M., BETHELL, F. H., ISAACS, RAPHAEL AND STURGIS. CYRUS.

*The Occurrence and Treatment of Neurologic Changes in Pernicious Anemia.* J. A. M. A., (December 1), 1934.

The authors present a study of a comparatively large group of pernicious anemia patients in whom there occurred neurologic and mental manifestations to determine the effect of various types of antianemic therapy on them.

Nervous system involvement has been noted in 89.2% of the four hundred and eight patients alive at the present time. Of these, 43.2% had the symptoms of cord changes at the onset of the disease and in the remainder the changes developed at some period during the course of the illness, but before the patient came under the authors' observation.

In a series of fifty of these patients especially studied, cerebral involvement occurred in 64%. The average duration of the disease in the entire group of patients before admission was about two years.

In spite of adequate antianemic therapy, improvement in symptoms of the central nervous system was observed in less than fifty per cent of the cases, and improvement in signs in about two per cent of the cases.

Antianemic therapy given in the sufficient amounts does not have a specific curative effect on spinal cord degeneration.

Genito-urinary infection, trophic ulcers and pneumonia with complicated marked central nervous system degeneration usually indicate a poor prognosis.

Francis D. Murphy, Milwaukee, Wis.

EVERSON, GLADYS J., AND DANIELS, AMY L.

*A Study of Manganese Retention in Children.* Journ. Nutrit., Vol. 8, No. 10, 1934, pp. 497-502.

A manganese retention study was made on seven small children (3 to 5 years old). Three diets containing manganese varying from 0.101 mg. per kilogram of weight to 0.304 mg. per kilogram of weight were used. All three diets contained meat, milk, eggs, bananas, potato, tomato, orange juice, and cod liver oil. The low and intermediate manganese diets differed only in the choice of cereal foods; white bread and oatmeal being used in the low manganese diet, while commercial whole wheat bread and whole wheat cereal were used in the intermediate diet. Foods that are particularly high in manganese were chosen for the high manganese diet.

The result of this study was that the amount of manganese retained was found to be proportional to the amount ingested. The writers feel that manganese is essential to the physiological development of children. Since the manganese content of the more usual foods consumed by man differ widely and since some diets for children consist largely of milk and refined cereals it is possible that these diets contain too little manganese.

It is suggested that children's diets should contain from 0.20 mg. to 0.30 mg. of manganese per kilogram of weight.

Clifford J. Barborka, Chicago.

KOEHLER, ALFRED E., AND ALLEN, SONIA E.

*Nutritive Value of Lactose.* Journ. Nutrit., Vol. 8, Oct. 10, 1934, pp. 377-383.

A study of the nutritive value of lactose, as compared with that of sucrose and glucose, was made on full grown

rats. The rats were first fattened on a calf meal diet, then placed in small individual cages and given a diet approximately 30% to 40% below maintenance. After the rats had lost 40 grams to 50 grams body weight—lactose, glucose or sucrose was added to the diet. The rats getting the lactose diet showed a slightly greater gain over those getting the sucrose or glucose diets for the first few days. However, after the fifth to the ninth day the weight gain was distinctly less on the lactose diet. Activity was not a factor in the poorer nutritive value of lactose since the voluntary activity of rats on a lactose diet was not greater than those on a glucose or sucrose diet.

Apparently a considerable portion of lactose ingested, approximately 40% to 50% is lost to the rat as far as weight or energy relationship are concerned.

Clifford J. Barborka, Chicago.

KISNER, PAUL; WEST, EDWARD S., AND KEY, J. ALBERT.

*Effect of Gelatine Feeding Upon Cases of Pseudohypertrophic Progressive Muscular Dystrophy.* Proc. Soc. Exp. Biol. and Med., 82:143-145, Nov. 10, 1934.

A study on the effect of prolonged gelatin feeding was made on three boys with well developed cases of pseudohypertrophic progressive muscular dystrophy.

Comparative results of gelatin feeding was made with that of glycine feeding. In both instances there was an increase of creatine over that of the control period. Creatine excretion on a meat free and gelatin free diet (after the gelatin feeding was over) was essentially the same as in the control period before gelatine feeding.

The investigation indicated that the general condition of the patients appeared better during the gelatin feeding. Gelatin feeding affords as much stimulation as glycine feeding in this condition, although the clinical examination of the muscles throughout the period of observation showed little changes—possibly some further degeneration.

Clifford J. Barborka, Chicago.

W. M. SKIPP.

*Pituitary Headache.* Endocrinology, 18, 5, Sept.-Oct., 1934, p. 596.

The author reviews briefly the subject of pituitary headache and reports 11 cases of which 10 occurred in women and 1 in man, an unusual occurrence. He quotes the explanation of its cause as given by the work of Doisy, Allen and Novak as being the waning of the gonad secretions at the end of the intermenstrual period, which liberates the pituitary from their checking influence and permits the gland to increase in size through over-activity. If the sella is small the hypertrophy may increase to the point of destruction of its walls, with possible involvement of the II, III, IV, V and VI cranial nerves. Cushing ascribes the pain to an increase of the intracapsular pressure of the pituitary; others, Leak, Lovenhart and Muelhberger (and more recently Adson—Proceedings of the staff Meetings of the Mayo Clinic—9, 45, Nov. 7, 1934; 673) to the irritation of the meningeal vessels. Relief was obtained promptly in all of the 11 cases by the subcutaneous injection, repeated at varying intervals, of  $\frac{1}{2}$  cc. of Infundin (B. & W. Co.). Two  $\frac{1}{2}$  grain tablets daily of pituitary posterior lobe gave less relief and the extract of the anterior lobe no relief whatsoever.

N. W. Jones, Portland, Oregon.



## SECTION IV—*Roentgenology*

### Cascade Stomach: A Review

By

ROY UPHAM, M.D., F.A.C.S.  
NEW YORK CITY, NEW YORK

A SURVEY of American literature on the subject of "cascade stomach" reveals scant mention of this condition. Cascade stomach has attracted far more attention in France, Italy and England than it has in this country.

#### DEFINITION

Cascade stomach is not a particular variety of "hour glass" stomach, as is considered by many, but is the result of a special change in form and position of the stomach. It has only one thing in common with hour glass stomach, that is, the division of the stomach into two parts. In cascade stomach there is a typical dilatation of the upper pocket with enlargement posteriorly into the upper posterior portion of the abdomen. It is characteristic of cascade stomach that the upper pocket is always larger than the lower pocket, and there is a distinct difference in the lumen. In hour glass stomach one pocket is situated above the other in a direct line, and there is an equal tonicity in both pockets, as well as nearly identical lumen outline. In cascade stomach the upper pocket lacks tonicity, the contents filling the upper pocket as though in a flaccid sac devoid of peristalsis. Hour glass stomach, in the lateral view under the fluoroscope, discloses but little posterior enlargement and displacement of the upper sac, and the anteroposterior diameter is a little in excess of the normal stomach; whereas, in cascade stomach there is a pronounced enlargement posteriorly of the upper sac, with the stomach far to the back of the abdomen. By a sudden change in the position of the patient the fluid contents in the toneless upper pocket can be made to change its level and a splashing is occasioned as of fluid in a cavity.

To Rieder (20) belongs the credit of first calling our attention to this condition in 1910, Assmann (1) giving him credit in his book "Die Roentgendiagnostik der Inneren Erkrankungen."

Le Wald (14) reports that he identified the condition as early as 1911 in a routine examination of some medical students at New York University and Bellevue Medical College. Le Wald termed the condition "shelf stomach."

Stierlin (23) reported the first two operations for cascade stomach in 1916. He found a callous ulcer at or near the lesser curvature with spasmodic indrawing of the greater curvature, producing deformity in each case.

Schlesinger (21) reported ten or twelve cases, finding some of the earlier instances of spasmodic cascade which disappeared with a resulting normal stomach. One of these appeared to be a reflex from duodenal ulcer, and an effort was made to parallel the condition of hour glass stomach, attention being called to the fact that there were intermittent forms in both and persistent forms in both. Schlesinger (21) endeavored to establish that intrinsic pathology might cause the condition, or that it might be a reflex from remote causes or conditions of the general nervous system.

Faulhaber (9) previously had had two cases, one of which clinically was diagnosed as gastric ulcer with hemorrhage, but at operation no ulcer was found. This case undoubtedly belongs to the type of cascade stomach which will be discussed in detail later in this article, and which is not due to intra-gastric pathology. In Faulhaber's (9) second case there was an ulcer with involvement of the pancreas, and in this case the pathology undoubtedly agrees with what is to be stressed by the writer later in this article.

Schutze (22) first distinctly reported the balloon form of the upper sac, which is characteristic of the condition. He was the first to emphasize the characteristic deformity with displacement upward of the left crus of the diaphragm, with concomitant displacement of the heart due to the dilatation of the fundus of the stomach by the fluid and gas contents. The constant upward displacement of the left crus of the diaphragm shows the excessive pressure produced by the obstruction, and at once confirms the hypothesis of a pressure-destruction of the fat in the upper left quadrant of the abdomen, further evidencing the pressure which may be exerted on the spleen, the colon, and the kidney—structures normally occupying the upper left quadrant of the abdomen. Comparing the upward pressure on the diaphragm with the hour glass, it is evident that only the nearly complete organic malignant obstruction could cause such a displacement of the left crus as is seen in nearly every case of cascade stomach. Therefore the deduction must be that the obstructive features of the cascade are of a very pronounced and obstinate character. Schutze seems to have had a particularly large experience with the condition, as he reports thirty to forty cases, and classes the deformity as dependent upon an anatomical basis.

Laurel (13) made a contribution when he drew attention to the transitory forms as differing from the true cascade stomach of pathological significance. In the course of routine methods of investigation the writer has observed the spasmodic type with a fair degree of frequency; and if the etiology of the spasmodic type is that suggested by Barclay, (2) namely, a spasm of the oblique muscle of the stomach drawing the stomach up, it can readily be understood how such a transitory cascade can occur. Laurel (13) considers this as a normal cascade form of stomach in contradistinction to the cascade form produced by a gas-filled colon, either through pressure which causes the stomach to ride above (which etiology is not complete, although it may be a partial element), or by traction of the colon. There is a cascade stomach of pathological significance; the cascade caused by gastric ulcer with cicatricial or cord formation, and cascade stomach due to malignancy.

Assmann, (1) in his work on radiographic diagnosis, agrees that gaseous distension of the splenic flexure of the colon is a significant etiological factor. In one of his cases there was marked distension of the splenic flexure of the colon, and at post mortem the stomach was found to be normal. In another case there was a diaphragmatic hernia with extreme gaseous distension of the colon, the result of tubercular peritonitis. Later, this case presented a normal stomach. In a third case of cascade stomach occurring in adhesive peritonitis, at autopsy the stomach was found to be normal.

Barclay of England, (2) in presenting the name "cup and spill" stomach in 1921, brought forward the suggestion of a spasm of the oblique muscle fibers as an etiological factor.

The cases reported by Stupel (24) all depended upon recognized pathology. His first case presented a tumor in the left hypochondrium, which was reduced by x-ray treatment, and the stomach returned to normal appearance. In his second case there was a congenital transposition of the caecum and ascending colon to the left with a chronic appendix. His third case had a diaphragmatic hernia on the right side, with upward displacement of the colon and liver.

Wilucki (27) brought out the point that extraventricular tumor in the region of the splenic flexure may act as a causal factor. He, also, was at a loss to explain the etiology, believing that spasm from gastric ulcer or reflex spasm from duodenal ulcer, or adhesions involving the stomach, could be a cause. There was also an extrinsic factor, such as gas in the colon. He particularly stresses the cicatrix of healed ulcer and the deformity of malignancy as intragastric causes.

Feissley and Fried (9) reported a case in a woman of fifty years who was operated upon twice, and still the cascade continued. At the first operation a short meso-colon was found, also a short hepatogastric ligament, and it was felt that the shortness of the ligament and adhesions about the gall-bladder explained the cascade stomach. After operation symptoms returned and two months later she was operated upon again with the same findings, except that the drawing up of the stomach was more pronounced. Neither atropin nor papaverin was of any avail. At the second laparotomy the findings were: omentum adherent to the abdominal wall, liver and surrounding structures; colon and gastro-colic ligament drawn upward. The

operation consisted of loosening the adhesions and liberating the colon and liver. A month later x-ray examination revealed that the cascade stomach was still present. The authors felt, in this case, that spasm could be excluded, as neither atropin nor papaverin had any effect. They believed aerophagy was a factor in distending the fornix of the stomach.

Webster (26) reported two cases, the first of which improved under medical treatment, and appeared to be of the spasmodic variety. His second case was one of extreme size of the two segments of the stomach, and was not affected by belladonna. At operation the stomach was found to be normal with extreme gaseous distension of the entire colon. There was a healed duodenal ulcer, and a gastroenterostomy was performed—the results not being definite. Webster also stresses the factor of spasm of the oblique muscle fibers.

Matthes (15) claims that the condition is the result of combined regional and diffuse spasticity of the stomach, and may be due to an ulcer on the lesser curvature at the seat of the spasm; that it also is encountered as the result of an enlarged spleen with gas in the splenic flexure of the colon and transverse colon, and from duodenal ulcer, and he emphasizes the fact that at times it may be due purely to spasm.

Ratkoczi (16) feels that the cascade stomach is actually a roentgenological conception, stressing that it is not a special variety of hour glass stomach. The contrast meal forms in a high-lying, bowl-shaped sac which is very much larger than the tube-shaped lower part, which later becomes filled from the upper sac, the entire meal frequently remaining for minutes before it empties into the distal part. In hour glass stomach the upper sac is usually small and the greater part of the meal flows uninterruptedly into the mostly flaccid, but at all events larger, distal part of the stomach. Various peritoneal adhesions may give rise to peculiar changes in the shape of the stomach, but never give rise to changes in size and shape such as the cascade stomach. High up, immediately below the diaphragm and more dorsally in the lower part, lies the larger bowl-shaped part of the stomach, in which the greater part of the meal gathers following ingestion. To the right, and in front, comes the hose-shaped distal part, the direction being from behind and from the left towards the right. The central part, near the pylorus, unfolds slowly, and fills with an appearance of an elephant's trunk. The fact that the lower part of the stomach lies to the right can best be seen in the lateral position. As regards the etiology, he emphasizes more the question of the distension of the splenic flexure, but claims in cases of pressure by the splenic flexure the changes must be passive ones, and feels that the entire nature of the cascade stomach is against a passive concept. The shape of the cascade stomach is too variable, and changes too quickly.

Ratkoczi (16) refers to some experiments that were carried out by Schlemmer of Budapest, in which he inflated the colon and produced a type of cascade stomach, but only in cases where there was pathology in or about the stomach, never where the stomach was normal. In taking issue with the hypothesis of dam-



ming over the tail of the pancreas, Ratkoczi (16) states that this can occur in the recumbent, but not in the standing position. This conception, it seems to the writer, is very much in error, as the deformity can be maintained readily in the filled stomach in the erect posture.

Zollschan (29) emphasizes that the typical feature of cascade stomach lies in the fact that the pars media is not in direct continuity with the pars cardiaca. He, again, draws attention to the forcing outward of the left side of the dome of the diaphragm. He stresses the cascade-like overflowing of the contents from the fundus pocket into the lower pocket, and particularly emphasizes the line over which the fluid drops. He quotes the collaborated work of Macarque and Baize, who dealt with the problem in 1926. They explained the marked bulging of the fundus posteriorly on the ground of increased pressure due to swallowing of air and stretching of the stomach wall at this point. They did not develop the possibility of the dilatation being due to displacement of other organs. Zollschan (29) reports an extensive study of the models by His, Sr. at the Berlin Anatomical Institute. It seems to the writer that the first step in the explanation is His' finding that a changed position of the spleen—a lateral displacement—is a factor which allows the fundus to become dilated. This increase of space is followed by the second factor, namely, that the stomach passes far back of the ridge at the tail of the pancreas, and that the splenic artery, running from the celiac axis outward to the spleen, lies above the tail of the pancreas and forms a further bridge upon which the posterior wall of the stomach can be obstructed by pressure. This, with the increasing area of the stomach, causes pressure necrosis of the surrounding fat, with a further drop of the stomach over the ridge formed by the splenic artery, and increased obstruction. In the case of air-swallowing there is further dilatation of the upper part of the stomach with pressure upward of the diaphragm. In two of His' models, viewed from behind, is shown some bilocularity of the stomach due to the stomach lying on the pancreas. The stomach shows a shallow, but still plainly visible, retro-pancreatic pocket, together with a fold on the posterior surface of the stomach. This was described by His, and named by him "*plica pancreatico angularis*." The factor of displacement of the spleen may be one of negative pressure in the abdomen, and, as has been noted in this article, the colon may create a similar condition by an increased positive pressure. In several cases the writer has observed the splenic flexure passing up to an abnormal position directly below the diaphragm; then, with distension, a pressure is exerted which forces the stomach backward, pushing over the upper border of the pancreas, and thus producing the obstruction to induce the cascade stomach.

At this point it seems appropriate that the particular findings in one of the cases recently seen by the writer, and verified by operation, should be mentioned. At operation the stomach was found to be perfectly normal, but the phrenico-gastric ligament was entirely absent, and the only support of the stomach was at the cardia. This, coupled with an improperly fixed spleen, allowed it to drop into a lower position, thus permitting the condition of affairs to

arise, which, in the opinion of the author, is the cause of cascade stomach—first, a factor of abnormal mobility of the fornix, which, in this case, was the absence of the phrenico-gastric ligament. This mobility permits the stomach to prolapse posteriorly and rotating on the splenic artery and the tail of the pancreas, causes the damming behind which the cup forms and the fluid cascades into the lower pocket. With the increased pressure, aerophagy becomes the routine practice of the individual with increased pressure and dilatation of the stomach in the posterior area of the fornix, where the circular muscle fibers are poorly developed. The normal stomach, being fixed posteriorly to the diaphragm and to the spleen, possesses a support that is lacking in the free fornix, and this probably is an element which prevents dilatation, but with a free, mobile fornix dilatation readily takes place.

This description explains the physical factors by which cascade stomach is acquired, and in the cases that are accompanied by pathology within the stomach, the pathology gives rise to perverted motor functions which produce a similar condition. It is possible, as before mentioned, that the colon may produce the same series of results, where, as occurred in a second case, the spleen is prolapsed and the colon extends up to the left crest of the diaphragm and is rotated in towards the median line, producing backward pressure on the upper part of the stomach, and producing the same rotation about the splenic artery and the tail of the pancreas.

Barclay, (2) in his recent book, still stresses the "cup and spill" stomach as being due to a spasm of the oblique muscle fibers. He states that he believes the possible action of this oblique muscle band may be the clue to the problem, and that if its contraction should be shown to be independent of those of the other coats, a basis would be provided for the explanation of the various forms of cascade stomach. He states that in some subjects, nearly always men, the angle over the left kidney is quite sharp, perhaps 70 degrees, so that the upper portion forms an exact cup, while the lower two-thirds of the organ drop down straight. These stomachs fill in a peculiar manner; the upper cup fills first and the food appears to spill over into the lower part, hence the name "cup-and-spill," cascade or "drain trap." The food usually comes straight forward over the brim and sometimes spills to the inner, sometimes to the outer side. The "cup-and-spill" appearance may be associated with duodenal lesions or with a gastric ulcer high up on some part of the wall. However, it does not appear to be abnormal, but a variation in normal form. Very often it is merely transitory.

Zollschan (29) dwells a good deal on the constriction of the diaphragm and the ridges which occur upon it from different development, and from the forces incident to pressure of the large fundus. One important point he brings out is that if the diaphragm is up very high, the fundus of the stomach rises much higher than normal, and that the cardia, being fixed, may become twisted upon itself and close like a valve, preventing any gas from escaping. He again stresses the necessity of an oblique view of the stomach showing that the posterior enlargement is a particular diagnostic feature of the cascade.

The French use the appellation "champagne cup" stomach because of the large sac in the upper part, the lower segment being tubular.

Brohn (4) emphasizes the pressure of the colon as the factor that produces the condition by distension and pressure, forcing the stomach backward upon the dam, but the author feels that he misses the condition of the abnormal mobility of the stomach. A further attempt has been to develop a twisting of the stomach upon its axis as a casual factor. Andre Dumont (8) states that "everything happens as if the stomach were pivoting on a transverse axis, going from the midline to the left side of the abdomen, passing in front of the vertical column a little lower than the level of the cardia. The stomach is found in front of this line, which it touches by its posterior wall, and in order to form the appearance of a cascade, it seems to swing from front to back, making a fold on its axis. In the more advanced stage the displacement of the stomach from front to back and top to bottom is increased. In the extreme stage the posterior basin becomes a true sac formed by almost the entire stomach." But, here again, there is not sufficient emphasis placed upon the fact of the probable congenital abnormality whereby the fornix of the stomach is not attached to the diaphragm.

### SYMPTOMATOLOGY

Pronounced distension and fullness with aerophagy and belching, and the characteristic feature that the patient, in most cases, is practically entirely relieved of symptoms by lying on the left side, which usually allows the upper cup of the stomach to empty. In some cases the emptying of the upper pocket is at the lesser curvature side, while in other cases it is at the greater curvature side. Sometimes the spill is over the center of the dam, but characteristic of the writer's cases has been the relief of distress on assuming the recumbent position, particularly lying on the left side.

On physical examination the characteristic findings are an abnormal prominence of the eighth, ninth and tenth ribs on the left side with an abnormal fullness of the left hypochondrium. Where the condition is pronounced, the actual distension amounts to two or three centimeters.

Absolute diagnosis, of course, is made by means of roentgen-ray examination. Because of the fact that the two pockets in some measure overlies, undoubtedly some of these cases have escaped attention, and it should be a routine practice to examine all stomachs fluoroscopically in the left lateral position. If this is done the large posterior distension of the stomach becomes evident, and the upper posterior sac can be seen extending well toward the back.

Redding (17) describes the filling by stating that if such a stomach is observed during the ingestion of the opaque meal it will be noted that the fluid collects in a wide cul-de-sac which is formed by a downward projection of the entire posterior aspect of the stomach at the level of the cardiac orifice. When this cul-de-sac is filled, the meal spills over its anterior border to cannulize the remainder of the gastric lumen. This condition, he asserts, is best demonstrated by a lateral or oblique position of the patient.

The differential diagnosis from a diverticulum of the stomach must be borne in mind, but the characteristic findings previously outlined, with the extreme size of the upper sac of the cascade stomach, will make the diagnosis apparent.

Characteristic is the level of fluid which readily can be made to splash upon agitation of the patient, and the change in shape and position on deep inspiration.

### TREATMENT

Detailed study of the treatment suggests that in the early spasmodic cases the usual anti-spasmodics may be of value. Otherwise, medically there is little that appears to be of definite value. From a review of the literature and report of the operations, the cases which have been devoid of intrinsic pathology in the stomach have been very unsatisfactory from an operative standpoint. Recurrences have taken place when adhesions were liberated, and in some instances operation has been repeated, with similar lack of success. Where the condition is spasmodic and reflex from the gall-bladder or from duodenal ulcer, attention to the exact pathology by appropriate surgical measures has brought relief from the condition; but where there is a well-defined dilatation posteriorly in a stomach that is devoid of the phrenicogastric ligament, anchoring of the upper surface of the fornix to the under surface of the diaphragm is presented as the only surgery that will overcome the posterior dilatation and extension of the upper surface of the fornix, the free movement of which allows the dropping down of the fundus behind the splenic artery and the tail of the pancreas, thus producing obstruction. Posterior gastroenterostomy, of course, is not practicable, but an anterior anastomosis with enteroenterostomy might be suggested if the superior pocket can be delineated.

As much of this pathology is due to spasm and obstruction, when the stomach is empty on the operating table, it is difficult to demonstrate the exact conditions present. As Zollschan (29) states: "It ought not to cause any surprise that all the relationships have escaped detection heretofore. Both the description and pathological anatomy fail to explain these anomalies as regards shape for the reason that only the tonus of the living organism can show the variations. During surgical intervention the tonus is changed by anesthesia." He states that proper credit must be given to the x-ray because that alone can show the condition during life, and further study by the x-ray, in conjunction with the anatomical laboratory, may deduce new anatomical facts because with the x-ray the organs are seen with their proper tone during their lifetime in their physiological, pathological relations and functions.

If these cases can be verified by a study at operation or necropsy (and we expect, with a knowledge of these hypotheses, they may be) it will establish the hypothesis that we have advanced relative to the acquired or congenital lack of the phrenico-gastric ligament with free mobility of the fundus and the ability of the

stomach to prolapse into a posterior position, where aerophagy and food stasis produce dilatation, which induces a further prolapse over the dam formed by the splenic artery and the tail of the pancreas, intensified by pressure necrosis and increased dilatation of the fundus, and obstruction at the point of damming, giving rise to the condition we recognize as cascade stomach.

Discussions of cascade stomach in the English language are very meager, and it was for that reason that the preparation of this review was prompted.

#### ACKNOWLEDGMENT

The author wishes to express his appreciation of the courtesy extended to him by Dr. Le Wald in placing at his disposal his unpublished paper and certain translations on the subject discussed in this article.

#### REFERENCES

1. Assmann, H.: *Die Roentgendagnostik der inneren Erkrankungen*. Leipzig, 1921, S. 363.
2. Assmann, H.: "Cascade Stomach," 1929.
3. Barclay, A. E.: *Lancet*, 1921-11, p. 648.
4. Blockert: *Deutsch Med. Wochschr.* 59-532-533, Apr. 7, 1933.
5. Broha, G.: *Arch. D. Mol. de l'app. digestif*, 23-118-122, Jan., 1933.
6. Carman, R. D.: "The Roentgen Diagnosis of Diseases of the Alimentary Canal," Saunders 1930 (2nd Ed.) p. 339.
7. Charnet, G. G.: *J. de Radio et d'Electrol.* 14-321, June 30.
8. Crohn: "Affections of the Stomach," p. 175-9.
9. Dumont, Mandel: "Note on the subject 'de l'estomach en cascade.'" *La Policlinique*, Mar., 1932.
10. Faulhaber, M.: "Zur Diagnose und Behandlung des Chronischen Uleus Pylori." *Much Med. Wochschr.* 1913, Nr. 17 and 18.
11. Feissley, H., and Fried, A.: "Etiology of the Cascade Stomach," from *Fortschritte auf dem Gebiete der Röntgenstrahlen*, Hamburg. Publishers Lucas Grafe & Sillem, 1922, Academy of Medicine 130674, page 237, XXIX, 2.
12. Feissley, R., and Fried, A.: *Zur Atiologie des Kaskaden-magen*, *Fortschritte B.D.* 29, 1922.
13. Golob, Meyer: "Cascade or Winterfall Stomach." *Am. Jour. Roentgenology and Radium Therapy*. Nov., 1929, p. 451-454.
14. Kochler: "Roentgenology." Pub. by Wm. Wood, p. 442.
15. Laurel, H.: "Ueber den sogenannten Kaskaden-magen." *Deutsch Med. Wochschr.* 1920, Nr. 47, S. 1300.
16. Le Wald, L. T.: "Cascade Stomach. Differential Diagnosis from Carcinoma of the Cardia." Read at Annual Meeting of the Radiological Society of North America, Nov. 30, 1932.
17. Matthes, M.: *Textbook of Differential Diagnosis of Internal Medicine*. Trans. by I. W. Hild and M. H. Gross, P. Blakiston's Son & Co., Philadelphia, 1925.
18. Rathkozi, N.: "Etiology and Diagnostic Meaning of the Cascade Stomach," *Fortschritte auf dem Gebiete der Röntgenstrahlen*. N. Y. Acad. of Med., p. 593-1931-43. (Nander Rathkozi, University Roentgenabteilungsleiter, Mit 17 Abbildungen).
19. Redding, J. Magnus: "X-ray Diagnosis," a manual for Surgeons, Practitioners and Students. Pub. by Wm. Wood & Co., N. Y., p. 171.
20. "Abnormalities of Gastric Tone and Position." J. Magnus Redding, F.R.C.S., Sr., Radiologist in Guy's Hospital.
21. Revesz, V.: "Der Reltende-magen." *Fortschritte B.D.* 29, 1922.
22. Regelsberger, H.: *Ergebn. d. Med. Strahlenforsch.* 5-1-20-31.
23. Rieder, H.: Quoted by Assmann v. Wilucki. (*Die Sanduhrformen des Menschlichen Magens*. Wiesbaden, 1910).
24. Schlesinger, E.: "Die Roentgendagnostik der Magen und Darmkrankheiten," Berlin, Urban und Schw., 1917.
25. Schlesinger, E.: "Über den Spitzischen Kaskaden-magen." *Fortschritte B.D.* 27, 1920.
26. Schutze, J.: "Ueber Kaskadenmagen." *Deutsch Med. Wochschr.* 1920, Nr. 24.
27. Stierlin: "Klin. Roentgendagnostik des Verdauungsknnns." Wiesbaden, 1916, S. 146.
28. Stupel, R.: "Zur Atiologie des Sogenannten Kaskadenmagens." *Fortschr. a.d. Geb. d. Roent.*, 1921 Bd. 28, H. 3, S. 229.
29. Torelli, G.: "Casende Stomach Occurring After Phrenico Exerests." (G. Torelli, Lecto contra la Tubercle, 4-473, May, 1933).
30. Webster, J. H. Douglas: *Phys. in charge of Physical Medicine Dept., Middlesex Hospital. A Contribution to the Congress of Radiology and Physiotherapy*, London, June 7, 1922.
31. Webster, J. H. D., M.R.C., C.P.E.: *Archives of Radiology and Electrotherapy*. The Official Organ of the British Ass'n. of Radiology & Physiotherapy. Vol. XXVII, June, 1922, to May, 1923.
32. Wilucki, V.: "Ein Fall von Kaskadenmagen, bedingt durch extracirculären Tumor." *Munch. Med. Wochschr.*, 1918, Bd. 65, S. 851.
33. Zehbe: "Ueber Kaskadenmagen." *Fortschr. a. d. Geb. d. Roent.*, 1917, Bd. 25, H. 2, S. 107.
34. Zehbe: "Ueber Kaskaden-magen." *Fortschr. Bd.* 24, 1917.
35. Zollschna, J.: "Etiology of Cascade Stomach," trans. by Dr. Viggo A. Christensen, J. Zollschna, Carlsbad, Germany.
36. J'Arendt Med. Klin.: "1932 Retrogastric extravasation of blood with development of Cascade Stomach." *Analysis of Roentgenograms*. J. Arendt Med. Klin., 27-1859-1861. Dec., 1831.
37. L'Echo Medient Du Nord: "Estomach en Cascade," 35, p. 379, Aug. 6, 1933.

## ABSTRACTS

STEWART, W. H., AND ILLICK, H. E.

*Roentgen Diagnosis of Carcinoma at the Cardia, Am. Jour. Roentgenol.*, xxxii, July, 1934, pp. 43-51.

The authors direct attention to the relative frequency of carcinoma of the cardia end of the stomach, they discuss methods of examining this region roentgenologically and they consider some problems in the differential diagnosis with the hope that roentgenologists will be able to assist in the early recognition of the disease. The situation of the carcinoma may make detection difficult, and this applies especially to involvement of the upper pole of the stomach. Pyloric carcinoma comprises about a half of all cases of carcinoma of the stomach, and obstructive symptoms may be prominent early. Carcinoma of the body of the stomach comprises about a third of all cases, and it generally remains undiagnosed until the condition has become inoperable. Carcinoma of the cardia is seldom diagnosed or suspected until dysphagia is present.

In the technic of roentgenologic examination of the stomach careful preparation of the patient is essential, and it is most important that the stomach be as nearly empty as possible when the examination is conducted. A

careful, preliminary roentgenoscopic examination of the chest is made to rule out the presence of lesions above the diaphragm. Examination of the esophagus is then begun by having the patient swallow a small amount of a mixture of matzoon and barium, of a creamy consistency. The patient is rotated into the right oblique position to demonstrate best the postcardiac space. The examination of the stomach is begun before the barium is given, during preliminary roentgenoscopy of the chest; the left side of the diaphragm is watched during several examinations, and the left upper quadrant is observed for any perceptible fluid level in the stomach. The real examination of the stomach, and especially of the cardia portion, begins after the first swallow of barium enters the stomach. This barium should immediately enter the lower pole of the stomach, outlining the rugae of the midportion and collecting in a pool in the lower end; this leaves the cardia end outlined by a gas bubble. By palpation the entire stomach is then outlined under the screen so that the pliability of the gastric wall can be tested. At this time, the gastric mucosa is studied. If organic disease is present, there is marked irregularity, an abnormal bizarre

pattern, or actual loss of relief markings, in place of the normal stripe-like appearance alternating with ribbons of barium that fill the valleys between the rugae. The patient is given about a pint of barium solution to distend the stomach fully, and is then examined at this time, between two and four hours later, and six hours later.

The ten roentgenologic signs of involvement of the cardiac end of the stomach by carcinoma are as follows: 1. Any dilatation of the lower portion of the esophagus. 2. Any abnormal retention of barium in the lower portion of the esophagus. 3. Barium passing through the esophageal orifice in a continuous stream. 4. A narrowed esophagus, and unchanging canalization through the tumor. 5. A frozen mass, infiltration preventing the normal movements of the lower portion of the esophagus. 6. A mass visible in the gas bubble, or deformation of the magenblase. 7. A mass visible after the first swallow of barium, with a distorted rugal pattern, or a mass visible after distention of the stomach by a full meal, and with contracted lumen. 8. Barium forking over the mass. 9. Gastric hypermotility. 10. Esophageal antiperistalsis.

Dysphagia is found in more than half of the cases of carcinoma at the cardia. The most common history is slight loss of weight, fatigue, belching, nausea, anorexia, and mild epigastric distress after eating; occasionally, there is real pain and vomiting. Cardiaspasm is distinguished from carcinoma of the cardia by the typically cone-shaped filling defect, with smooth margins, which is situated above the diaphragm. Greater dilatation is present than with carcinoma of the cardia, and the clinical history of the duration of the complaint is longer.

Diverticulum of the lower portion of the esophagus is rare. Varix, causing a notching of the edge of the lower esophageal outline, and masses of varices that produce characteristic filling defects of the lumen, are often difficult to differentiate.

Lesions causing outside pressure, such as those resulting from metastasis, are usually differentiated roentgenoscopically.

Hernia of the stomach through the diaphragm must also be considered in the differential diagnosis. Benign ulcer of the cardiac end of the stomach is differentiated by radial striation of the folds, the small crater, and finally by its response to medical treatment.

K. Vinson, Rochester, Minn.

H. S. SOUTAR.

*Cancer of the esophagus, British Med. Jour., Vol. 2, Nov. 3, 1924, pp. 797-800.*

Carcinoma of the esophagus accounts for from 4 to 6 per cent of all malignant diseases. In England, the annual mortality from carcinoma of the esophagus is about 1600, 1200 of the persons who succumb to the disease being men and 400 women. Among men it is a disease of later life; 90 per cent of the patients are more than fifty years of age and far more commonly the lesions is in the lower two-thirds of the esophagus. Among women the disease may occur much earlier, and 50 per cent of the lesions are in the upper portion of the esophagus.

Histologically, carcinoma of the esophagus is almost invariably a squamous cell epithelioma and it is highly malignant.

In the majority of cases the first symptom is dysphagia, beginning with solid foods. This dysphagia usually is gradual in onset and is without remission. In a few cases in which the growth is at the lower end of the esophagus, the symptoms are rather those of flatulent dyspepsia, a feeling of fullness after meals, and eructation of gas. Pain is not an early symptom, but a reflex spasm, which results from attempts to swallow, may lead to acute discomfort. Hoarseness and aphonia may occur from involvement of one of the recurrent laryngeal nerves. Involvement

of the respiratory passages produces the most important group of secondary symptoms. Wasting occurs from starvation and the patient suffers severely from hunger and thirst.

Of the methods of examination, roentgenoscopy and esophagoscopy are described. The author is of the opinion that the passage of bougies is both useless and dangerous. Roentgenologic examination is best, as it is simple and safe. It will indicate the level of an organic obstruction and, in the majority of cases, will give indisputable evidence of the nature of the lesion. After a barium meal is swallowed and a certain quantity of it enters the stomach, the patient is placed in a high Trendelenburg position and the flow of barium from the stomach into the lower portion of the esophagus is observed. In this way, the extent of the stricture accurately can be defined.

Direct examination with the esophagoscope is undertaken to ascertain the character of the growth and the possibilities of treatment rather than for the diagnosis of a malignant stricture. Occasionally, it may be practicable to remove a fragment of growth for section, although it is not advised as a routine procedure.

The depth at which the esophagus lies, the fragile nature of its wall, the complexity of the structures by which it is surrounded, and the age at which the disease occurs, are all contraindications to surgical attack.

The main treatment of carcinoma of the esophagus consists of relief of the dysphagia which is accomplished by three methods: dilatation, intubation, and gastrostomy. Gastrostomy is usually done after failure of the other methods, although in certain cases in which the patient's condition is desperate gastrostomy is done first.

Dilatation should be attempted under the direct control of the esophagoscope. A fine, flexible bougie, on the end of a long steel wire, is passed first, and over this are passed tubular dilators of increasing size. Dilatation is usually followed by immediate relief of the dysphagia; the dysphagia, however, is likely to recur in a few weeks' time.

The author advocates intubation for malignant strictures. He has devised a flexible tube which is formed of a spiral of German silver wire with an expanded upper end and a twisted oval section that prevents upward displacement. These tubes are now in general use and are readily tolerated, the patient usually being unconscious of their presence; the large lumen permits the passage of ordinary foods. The tube is introduced with a large cone of gelatine in the end to facilitate passage through the stricture.

Cure of the disease is to be hoped for only with some form of radiation. The most direct method is insertion into the lumen of the tumor of a sound containing radium. When intubation with this spiral tube has been effected, it may be used for support of the radium. Another method is the introduction of radon seeds into the substance of the growth itself. In a few cases, a fairly satisfactory result has been obtained and the patient has recovered his power of swallowing; in no case, however, has a cure been effected.

Results of great interest recently have been obtained by Levett who used deep roentgen therapy; the rays were of short wave length and were limited to a narrow field. It is still too early to speak with any certainty of the results; in a few cases, however, it would seem that complete healing has been obtained without secondary stenosis. Another method the author is at present investigating is the application of radon to the outer surface of the esophagus after exposure by transthoracic exploration.

In conclusion, it is stated that, for the present, relief of dysphagia is regarded as the one object to aim at in treatment, and introduction of the spiral tube is the method most likely to achieve this result.

K. Vinson, Rochester, Minn.

## SECTION V—*Therapeutics*

### Therapy of Non-Malignant Biliary Tract Lesions

By

ALLEN O. WHIPPLE, M.D.  
NEW YORK CITY, NEW YORK

THE confusion that exists in the profession as regards the therapy of biliary tract disease is most unfortunate. There are radical surgeons who claim that all questionable gall bladders should be removed, and in the course of any upper abdominal operation, as for ulcer, excise the gall bladder as a routine. We cannot agree with this group at all in classing the gall bladder with the appendix as a vestigial pouch to be gotten rid of routinely. In addition there is a fairly large group of medical men who have a mistaken concept of the gall bladder as a nidus or focus of infection, and when every other focus, such as teeth, tonsils and sinuses, has been eliminated, pick on the gall bladder as a focus to be removed irrespective of whether it is giving symptoms or is the seat of definite inflammation. Opposed to these radicals are the conservatives, who discourage and delay surgery in the obviously diseased and chronically inflamed biliary tract until the patient, either because of unbearable repeated attacks of colic, or because of complete and unremitting common duct obstruction, develops an alarming Charcot's syndrome of chills, steeple temperature and deep jaundice, pleads for help, and the family insists upon operative relief. The writer has frequently heard the family physician stubbornly question the diagnosis of gall stones because the patient had not shown jaundice, showing his ignorance of biliary tract pathology, and exposing his general attitude toward its therapy.

The policy of delaying surgery in patients with well established and demonstrated gall bladder pathology until the inflammatory or obstructive factor has extended beyond the original site into the ducts, liver and pancreas, when urgent and unavoidable surgery carries with it a high morbidity and mortality, explains the dread of biliary surgery in the minds of the lay public as well as the medical profession. This will be demonstrated in the Tables which follow later.

There is a very safe and rational course to be followed between the unsound therapy of the extremes just mentioned. Modern accuracy in the diagnosis of biliary tract disease, and well defined therapy, now tested by many careful follow-up studies, leaves little excuse for the unsound views of the radical, or the shilly-shallying, dangerous attitude of the ignorant conservative practitioner.

In presenting our views on the therapy of biliary tract disease we wish to emphasize the rôle of the

three factors that enter into the pathogenesis of all cases of biliary tract disease requiring surgical therapy. These are (1) gall stone formation, the result of disturbed metabolism; (2) infection; and (3) obstruction. Singly or in combination, these are always present, and the part of the biliary tract where they are active determines the symptoms and physical signs. An understanding of these factors and their presence in the gall bladder or ducts makes the pathology, symptomatology, diagnosis and treatment of biliary tract disease rational, interesting, and accurate.

Based upon such an understanding we wish to present certain principles of therapy.

First, regarding the acute lesions: We believe that if the signs of acute cholecystitis do not subside promptly within 24-48 hours, under a regime of rest in bed, nothing by mouth except hot water and tea, with an ice bag to the right upper quadrant, then the gall bladder should be removed or drained. This is especially true if there is a spread of the area of right upper quadrant tenderness and muscular rigidity, indicating a beginning peri-cholecystic peritonitis. At this early stage a cholecystectomy is more feasible and the necessity of drainage with subsequent cholecystectomy is less likely. We realize that this policy is somewhat radical, and a change on our part from a conservative attitude, but our experience of the last five years in dealing with cases of acute cholecystitis bears out the opinion of many of the surgeons who have recently advocated early cholecystectomy in acute cholecystitis. The Author is certain that the relatively high mortality in the cases of acute cholecystitis in his own series was due to the earlier policy of delaying surgery until an empyema or cholangitis had made operation imperative.

As regards the chronic lesions: We believe that conservative therapy is preferable to surgery in the majority of cases of chronic cholecystitis, unless there is positive evidence in the history of biliary colic and typical interval digestive disturbances, such as bloating and belching, plus corroborative X-ray evidence of gall stones or non-visualization of the gall bladder by cholecystography. By conservative therapy we mean: 1. A careful dietary regime, excluding fried or greasy food, rich sauces, vegetables tasted after ingestion, such as cabbage and onions, fresh breads, and foods rich in lipoids and nucleo-protein with high cholesterol content. 2. Patients should be cautioned against over fatigue and especially against eating a

\*From the Department of Surgery, Columbia University.  
Submitted January 5, 1935.

heavy meal when fatigued. The findings of cholesterol crystals, calcium bilirubin particles and pus cells with bacteria in the duodenal contents obtained by duodenal intubation is, in our experience, even more reliable than cholecystography in demonstrating true pathology, that is, a lesion requiring surgical therapy. In many patients a failure of the gall bladder to take the dye or to empty it, indicates disturbed physiology of

the great majority of cases, if done while the lesion is limited to the gall bladder.

In our 62 cases of carcinoma of the gall bladder, 52 per cent have shown gall stones and chronic cholecystitis of long standing. I have never seen carcinoma of the gall bladder in an otherwise normal gall bladder. This form of malignancy is practically always fatal. Its almost invariable association with gall stones should give pause to those physicians who watch patients for years with known gall stone disease.

In the patients with inflammation or obstruction in the biliary tract beyond the gall bladder: In these cases surgery is, as a rule, urgent because of the dangers of jaundice, cholangitis, and pancreatic involvement. To delay surgical interference until the patient is deeply jaundiced, has a biliary cirrhosis, a prolonged clotting time and damaged kidneys, is

TABLE I

|                                                            | Total Cases | Died | % Mortality |
|------------------------------------------------------------|-------------|------|-------------|
| Acute Cholecystitis                                        | 54          | 7    | 13          |
| With Stones                                                | 43          | 4    | 9.3         |
| Without Stones                                             | 11          | 3    | 27          |
| Chronic Cholecystitis                                      | 410         | 4    | .98         |
| With Stones                                                | 320         | 4    | 1.2         |
| Without Stones                                             | 90          | 0    | 0           |
| Acute and Chronic Cholecystitis With Stones in Common Duct | 76          | 21   | 27          |
| TOTAL CASES                                                | 540         | 32   | 6           |

the gall bladder, but does not necessarily indicate a gall bladder requiring surgical removal.

When, however, there is strong evidence of gall stone formation or cholesterosis of the gall bladder in the work-up of the patient, cholecystectomy is the surest remedy because it removes the source of the trouble, and carries with it a low risk and a permanent cure in

TABLE II

|                                                      |      |
|------------------------------------------------------|------|
| Total Cases of Biliary Tract Diseases Operated . . . | 540  |
| Patients Surviving Operation . . . . .               | 508  |
| Patients Followed After Operation . . . . .          | 481  |
| Percentage of Followed Patients . . . . .            | 94.5 |

negligence that might be given a significant adjective.

These cases of jaundice, damaged liver and kidneys require several days of pre-operative therapy with glucose, saline and blood infusion, and most careful post-operative care.

The value of any therapy is determined by the immediate and late results, that is, in the surgery of the biliary tract the immediate results are significant if the mortality of the operation is high or low; the late results, as determined by bona fide follow-up visits, are significant if a large majority of the patients are relieved of their symptoms.

In estimating results the writer is convinced that collected statistics are not so valuable as a smaller series of unselected consecutive cases, studied pre-

TABLE III

|                                                                    | F O L L O W E D |    |   |          |    |   |           |   |   |
|--------------------------------------------------------------------|-----------------|----|---|----------|----|---|-----------|---|---|
|                                                                    | Less than 1 yr. |    |   | 1-4 yrs. |    |   | 5-18 yrs. |   |   |
|                                                                    | C               | I  | F | C        | I  | F | C         | I | F |
| 298 cases Chronic Cholecystitis with Stones                        | 99              | 25 | 6 | 111      | 15 | 0 | 33        | 9 | 0 |
| Percentage Cured                                                   | 81.7            |    |   |          |    |   |           |   |   |
| Percentage Improved                                                | 16.3            |    |   |          |    |   |           |   |   |
| Percentage Failures                                                | 2.              |    |   |          |    |   |           |   |   |
| Cases with No Follow-Up                                            | 19              |    |   |          |    |   |           |   |   |
| 81 cases Chronic Cholecystitis without Stones                      | 25              | 9  | 4 | 20       | 9  | 3 | 9         | 2 | 0 |
| Percentage Cured                                                   | 66.7            |    |   |          |    |   |           |   |   |
| Percentage Improved                                                | 24.7            |    |   |          |    |   |           |   |   |
| Percentage Failures                                                | 8.6             |    |   |          |    |   |           |   |   |
| Cases with No Follow-Up                                            | 9               |    |   |          |    |   |           |   |   |
| 56 cases Cholecystitis with Stones in Gall Bladder and Common Duct | 6               | 1  | 4 | 32       | 2  | 3 | 6         | 2 | 0 |
| Percentage Cured                                                   | 81.             |    |   |          |    |   |           |   |   |
| Percentage Improved                                                | 6.              |    |   |          |    |   |           |   |   |
| Percentage Failures                                                | 13.             |    |   |          |    |   |           |   |   |
| Cases with No Follow-up                                            | 1               |    |   |          |    |   |           |   |   |
| 46 cases Acute Cholecystitis                                       | 10              | 2  | 1 | 20       | 1  | 0 | 9         | 2 | 1 |
| Percentage Cured                                                   | 84.8            |    |   |          |    |   |           |   |   |
| Percentage Improved                                                | 10.8            |    |   |          |    |   |           |   |   |
| Percentage Failures                                                | 4.4             |    |   |          |    |   |           |   |   |
| Cases with No Follow-Up                                            | 1               |    |   |          |    |   |           |   |   |



operatively, operated upon, and followed by one individual over a long period of time. For that reason I am presenting a study of 700 unselected, consecutive patients having biliary or pancreatic lesions operated upon by me during the twenty year period of 1914-1934.

Table I shows the division of these cases into the acute and chronic benign lesions, with and without stones in the gall bladder, the ducts, or both, with the mortality of the operations in each group. By mortality we mean a death in the operated patient from any cause, while the patient is in the hospital, even if the case had been transferred to the medical ward for special therapy.

Table II shows the percentage of patients followed. In this connection I would emphasize the importance of actual follow-up interviews and examinations. By this method only can accurate determinations of therapeutic results of any kind be obtained. It has been my experience that form letters or question-

naires can be very misleading, either because the patient does not wish to disappoint his surgeon or, more often, complains of symptoms under the heading of ill health, which have nothing whatsoever to do with the original system or syndrome treated.

Many of the follow-up patients continue to be air swallowers after biliary tract surgery, because of a long-standing cribbing habit, and complain of belching unless they have the habit corrected before leaving the hospital. This is not a persistent symptom and should not be put down as a failure to cure gall bladder disease. It is an example of the advantage of personal interview over questionnaire method of determining therapeutic results.

Table III shows the operative results in the three main divisions of non-malignant biliary tract disease, divided into three periods of 12 months or less, 1 to 4 years, and 5 to 18 years follow-up.

## ABSTRACTS

CALLOWAY, J. LAMAR.

"Epidemic Pleurodynia." *South. Med. Journ.*, 27:1019, 1921, Dec., 1934.

Epidemic pleurodynia, ("devil's grip," "devil's cluteh," or "epidemic myositis") is an acute infectious (?) disease characterized by a sudden onset of severe pain in the chest and epigastrium, particularly along the diaphragmatic attachment, accompanied by fever but presenting no significant gastrointestinal symptoms or pulmonary or pleural signs, and showing a relative leucopenia or normal white count. Improvement takes place in a few hours but recurrence is common. Either sex may be affected but the disease is more frequent in children than adults. While the disease itself is never fatal, its possibility should be borne in mind since it may simulate an acute abdomen and lead to unnecessary operation. A knowledge of the existence of an epidemic, the absence of nausea, vomiting and diarrhea, and the presence of a leucopenia should aid in differentiating these conditions. Tachycardia helps eliminate typhoid. The treatment is that of an acute pleurisy with close observation and repeated white count.

J. Duffy Hancock, Louisville, Ky.

REHFUSS, MARTIN E.

*Proteins Versus the Carbohydrates. J. A. M. A.*, 103: 1600 (November 24), 1934.

Food faddists have presumed that proteins and carbohydrates in the diet are incompatible because proteins require an acid medium for their digestion while carbohydrates require an alkali medium.

A study of the digestion of proteins and carbohydrates in the normal human stomach was made by the author and others some years ago. They found that the normal human stomach may be of several types. One may show a relatively slow type and another a rapid type of gastric digestion. The secretory response in these healthy subjects could also be divided into groups, some showing a tendency to a low secretory output, others to a presumed normal, and still others to a hypersecretory type of response. The most significant feature in these studies was the constancy of the type of gastric function, the individuals falling into one of these groups and maintaining his gastric type.

Food faddists point out that while the normal individual can digest practically everything, the same rules do not

apply to the chronic invalid. A group of chronic invalids, patients with nephritis, myocarditis, cholecystitis, angina pectoris, asthma, bronchiectasis and acute illnesses such as rheumatic fever and even pneumonia, were carefully studied with reference to the ability to digest protein and carbohydrate food. The studies brought out the fact that there was no incompatibility between protein and carbohydrate digestion in the human stomach, even in this type of chronic invalid.

Francis D. Murphy, Milwaukee, Wis.

HARRY F. GRAHAM, M.D.

*Free Omental Grafts—Abdominal Operations, Annals of Surgery*, Vol. 100, Nov., 1934.

1. Use thinnest and most vascular area of omentum available.
2. The graft should extend beyond the raw area to be covered.
3. The edges should be turned under.
4. Very fine catgut sutures are used and placed close together around the circumference of the graft.
5. The raw edge of the great omentum should be turned under and sutured and should not be left in a thick mass to form undesirable adhesions.
6. Resection of the entire omentum is avoided, for gastro-intestinal hemorrhage occurs in four per cent of total resection, with a mortality of fifty to sixty per cent, according to Karger of Bier's Clinic.

### CONCLUSIONS

- A. Union is complete in three days.
- B. New capillary have formed in four days.
- C. Grafts are almost completely absorbed in four months leaving the surface endothelium.
- D. Free omental grafts will live. They become adherent to the underlying attached structure, prevent adhesions to surrounding organs and at times even remain free from surface adhesions in the presence of pus.
- E. They are hemostatic.
- F. They aid in preserving peristalsis by prevention of cuppling and immobilizing adhesions.
- G. They strengthen weak suture lines and resist infection.

Charles T. Sturgeon, M.D., Los Angeles.



CONNELL, F. GREGORY.

"Partial Gastric Fundusectomy in Treatment of Peptic Ulcer." *S., G., and O.*, 59:786-788, Nov., 1934.

Partial fundusectomy, which results in a diminution of the acid secreting surface rather than the removal of the alkaline secreting ulcer bearing area, has the further advantage of not disturbing the antro-pyloro-duodeno mechanism.

It is indicated in peptic duodenal ulcer, peptic ulcer of the jejunum after gastroenterostomy and peptic ulcer of the stomach. In the latter instance, supplemental local resection is advisable because of potential malignant

change and all cases with organic pyloric obstruction will require additional operative procedure. Following the operation, there is a marked drop in the acidity of the gastric contents, but this soon returns to approximately normal. Experimental work quoted shows a definite delay in the appearance of marginal ulcers.

The operative technique is described and seven clinical cases are tabulated. This procedure seems to have a sound physiological basis for some cases at least, and we look forward with interest to further reports by the author and others.

J. Duffy Hancock, Louisville.

## SECTION VI—*Abdominal Surgery*

### Diagnosis and Treatment of Amebic Abscess of the Liver (A Study Based on 4,484 Collected and Personal Cases)

By

ALTON OCHSNER, M.D.

and

MICHAEL DeBAKEY, M.D.  
NEW ORLEANS, LOUISIANA

THE previous conception that amebic infection is a disease limited to the tropics has been invalidated by the recent epidemic, and it is now a well established fact that amebiasis occurs ubiquitously. Whereas authorities on amebiasis have for some time appreciated that the infection is prevalent in all climates, the general conception has been that the condition is limited to tropical countries. As early as 1902, Sir Leonard Rogers (1) objected to the term "tropical abscess" being used to denote the hepatic complications of amebiasis, maintaining that this complication occurred in other than tropical climates. Craig (2), in a recent collection of 49,336 cases of individuals examined in the United States, found that the incidence of positive infections with *Endameba histolytica* was 11.6 per cent. Craig (2) is of the opinion that between 5 and 10 per cent of the people of this country harbor the parasites. An erroneous conception also exists as regards the most frequent complications of amebiasis; namely, amebic hepatitis or abscess. Contrary to the general conception, amebic infections of the liver occur frequently in individuals in whom there is no clinical manifestation referable to the colon; i.e., amebic hepatitis or abscess can and frequently does occur even though there is no antecedent history of dysentery or other bowel symptoms. In a series of 52 cases reported elsewhere by us (3) there were 21 (40.3 per cent) in which a history of previous

diarrhea could not be obtained. In a group of 318 cases collected from the literature, including our own, there were 131 (41.1 per cent) in which no antecedent diarrhea had occurred. In our own series of cases, diarrhea was a symptom at the time of admission to the hospital in only 10 of the 52 cases, an incidence of 20 per cent. The relatively large number of patients with amebic hepatitis who give no history of a previous diarrhea may be accounted for on the basis of a slight amebic infection of the bowel and that limited to the right half of the colon, which would produce no diarrhea. The diarrhea encountered in amebiasis is the result of irritation and ulceration of the colon by the amebae. In those cases in which the lesion is limited to the left side of the colon, a relatively slight infection with an abnormal secretion of fluid results in frequent evacuations of watery stools. A lesion located in the right side of the colon, however, even though it may produce a similar exudation of fluid into the colon, is not associated with diarrhea because the fluid is absorbed in its passage to and through the uninvolved and normally functioning left side of the colon. Rogers (4) found in 13 of 36 autopsied cases that amebic ulcers were limited to the cecum and that in 4 more they extended only as far as the ascending colon. In nearly half the cases only the proximal fourth of the large bowel was involved. In 6 additional cases scars were found in the cecum and the ascending colon. Thus, in 23 of 36 cases, almost two-thirds, the lesion was limited to the cecum and

\*From the Departments of Surgery, Tulane University School of Medicine, Charity Hospital and Touro Infirmary, New Orleans.  
Submitted December 17, 1934.

ascending colon, indicating that during life the amebic infection was latent. This observation confirms the above statement that the absence of diarrhea in no way excludes an amebic infection of the colon.

### DIAGNOSIS

Amebic hepatitis should always be considered in a patient with a persistent enlargement of the liver associated with pyrexia. A history of previous diarrhea is confirmatory evidence, but the absence of such a history in no way eliminates the possibility of amebiasis. The presence of pain and tenderness in the right upper quadrant, especially limited to the liver or radiating to the right shoulder, is corroborative. Associated with these findings there is usually a moderate leucocytosis without concomitant proportionate increase in the polymorphonuclear leucocytes. Pain was the most prominent symptom encountered in our own series of cases, being present in 80 per cent of instances. Tenderness along the right costal margin was present in the same incidence. In our series the average white blood count was 14,000 and the polymorphonuclear leucocyte count 79 per cent. Rogers (1, 2, and 5) and Manson-Bahr and Willoughby (6) have emphasized that in amebic hepatic abscess there is a moderate increase in leucocytes as contrasted with the marked leucocytosis which is seen in bacterial hepatitis and abscess.

One of the most important reliable aids in the diagnosis of liver abscess is roentgenography. According to Granger (7) characteristic changes in the contour of the diaphragm are found in liver abscess and subphrenic infections. In uncomplicated liver abscess there is distinct bulging of the diaphragm and pointing upward into the lower lung field, which is almost pathognomonic of liver abscess. In a case with liver abscess complicated by a subphrenic abscess in addition to the elevation of the diaphragm there is an obliteration of the cardiophrenic angle in the anterior-posterior roentgenogram (Fig. 1) and obliteration of the anterior costophrenic angle in the lateral view (Fig. 2), whereas in subphrenic abscess originating in other lesions there is obliteration of the costophrenic angle in the anterior-posterior view and obliteration of the posterior costophrenic angle in the lateral roentgenogram. Pancoast (8), Dickinson (9), and Love (10) emphasize the importance of elevation and immobility of the diaphragm in amebic abscess of the liver. These authors stress the importance of fluoroscopy and examination of the patient in the upright position when such is possible. We have been able to corroborate Pancoast's (8) finding that lung reactions in subphrenic lesions are of importance when present and usually indicate an amebic infection, because these abscesses are most frequently found on the convex surface of the liver in close contact with the diaphragm. The value of x-ray in the diagnosis of amebic hepatic abscess is well exemplified in the series of cases reported elsewhere by us (3). In 57 cases in which x-rays were made diagnosis was positive in 50 (87.7 per cent).

If, in addition to the above mentioned positive findings, one finds in a careful examination of the stools either active amebae or encysted forms, a positive diagnosis of amebic hepatitis can be made. Here again, however, a negative finding does not eliminate amebiasis as a cause of liver involvement.

The diagnosis of amebic abscess of the liver can be definitely established by aspirating the typical "chocolate-sauce" pus from the liver. We agree with Constantini (11), Chen et al (12), and Manson-Bahr (13) that the obtaining of the chocolate-sauce pus on exploratory aspiration is pathognomonic of amebic abscess of the liver. Because of the danger of a secondary infection of an amebic abscess and because one can never definitely rule out a pyogenic abscess, it is important that exploratory aspiration be performed in such a way that a contamination of an uninvolved serous cavity not be done. We cannot agree with Young (14) that the danger of infecting the pleural or peritoneal cavity by aspiration has been overemphasized and are inclined to believe that Young is fortunate in being able to base his opinion upon observations made in uncomplicated amebic abscess. It is also imperative that the aspiration be done in the operating room so that if pyogenic microorganisms are found in the aspirated material, an immediate open drainage can be performed. In order to determine the presence or absence of pyogenic organisms a smear should be made immediately after aspiration and if a large number of such organisms are found, open drainage should be instituted. In those abscesses located posteriorly, it is important that the needle be introduced below the costophrenic angle and inserted upward into the abscess cavity. Under no circumstances should the pleural cavity be traversed, even though many are of the opinion that this precaution is not justified, because uncomplicated amebic abscesses are sterile. Ludlow (15) stresses the fact that in aspirating amebic abscess of the liver, the needle should not be introduced more than three to four inches because of the danger of injuring a large vessel. It is occasionally necessary to attempt multiple punctures before pus is encountered. If such is done, it is important to remove the needle entirely before introducing it rather than changing the direction of the needle at the original site in order to obviate extensive injury to the liver.

### TREATMENT

The majority of amebic abscesses of the liver are sterile. In 46 cases reported elsewhere by us (3) in which a statement was made concerning the bacteriologic examination of the pus obtained from the abscess, the pus was found to be sterile in 41 (89 per cent). In a series of 386 collected and personal cases there were 328 (83.9 per cent) in which the pus was sterile. As a large proportion of amebic abscesses of the liver are sterile, the avoidance of secondary infection by open drainage is imperative similarly as in non-infected tuberculous abscesses. As emphasized in our publication elsewhere (3), the prognosis in amebic abscess of the liver depends to a great extent upon the secondary infection of the abscess cavity and the type of treatment employed. Rogers (16) showed that the mortality rate of 56.8 per cent which was obtained in cases with open drainage was decreased to 14 per cent in those cases in which closed drainage was used. The value of closed drainage is shown in Chatterji's (17) series in which there was a mortality rate of 1.6 per cent. The greater mortality rate in those cases treated by open drainage was due undoubtedly to the secondary infection of the abscess cavity from which there is considerable absorption and extension of the



Fig. 1. Anterior-posterior roentgenogram of chest and diaphragm in amebic abscess of the liver (Case report). Note characteristic elevation of right leaf of diaphragm and obliteration of cardiophrenic angle.

The technic of aspiration depends considerably upon the clinical manifestations. In those cases in which there are localizing signs and pointing of the abscess, the aspirating needle should be introduced directly over the mass. Otherwise, the aspirating needle should be introduced in such a way that the pleural and peritoneal cavities are not traversed, which can be best accomplished by introducing the needle in the ninth intercostal space in the anterior axillary line and directing it upward, medially, and backward. Occasionally an abscess can be entered by introducing the needle below the twelfth rib and extending it upward and anteriorly. After pus has been obtained by means of the aspirating needle, it is frequently necessary to introduce a trocar in order to evacuate the abscess contents completely because of the thickness of the pus. Kilner (21) emphasizes that frequently the thick contents of the abscess will cause blockage of even a trocar, giving a false impression that the abscess has been evacuated. When the abscess cavity has been evacuated of its contents, it is neither necessary nor desirable to introduce any substance into the abscess cavity, as it has been shown by Rogers (5), Talbot (22), and Chatterji (23) that the use of irrigating solutions and amebicides is valueless. If an immediate smear of the abscess contents shows the presence of a large number of pyogenic micro-organisms, open drainage of the abscess should be done because of the secondary infection; otherwise, open drainage is definitely contraindicated.

Immediately after aspiration of the pus from the abscess, an intramuscular injection of emetine should be given, because following the release of tension within the abscess, according to Rogers (5) and Talbot (22), there occurs an exudation of lymph, containing the injected emetine, into the abscess. Emetine is administered in grain doses daily until from 6 to 10 (grams 0.39 to 0.65) grains have been given. According to Leake (24), emetine administered over any given period of time should not exceed 10 mg. per kilogram of body weight. The maximum dose for a patient weighing one hundred and fifty pounds would be approximately 10 grains. Emetine should be used cautiously, because as shown by Rinehart and Anderson (25), working in Leake's laboratory, it produces in the experimental animal severe injury to the cardiac muscle. Leake (26) is of the opinion that although the other amebicides, acetarsone, carbarsone, treparsol, chiniofon, and vioform are safer and more efficient in the treatment of intestinal amebiasis, they should not be used in amebic hepatitis and liver abscess, as they themselves are toxic to the liver.

#### CASE REPORT

A. S.: Admitted to a Medical Service, Charity Hospital, New Orleans, La., on 9/24/34 with a diagnosis of phthisis pulmonis.

White male—Age 53 years—Fisherman

C. C.: Pain in upper right quadrant of abdomen.

P. I.: Began to suffer from pain in upper right quadrant eleven weeks ago. Pain cramp-like in character, located just below costal margin. Has had this pain off and on for past eleven weeks. No pain on respiration. No

process into contiguous portions of the liver. Only by keeping the abscess cavity closed is there any possibility of maintaining the sterility of its contents. Secondary infection occurs following open drainage in spite of meticulous care being used to prevent contamination. The advantage of aspiration of the abscess combined with emetine therapy has been emphasized by many investigators (Manson-Bahr et al (18), Thurston (19), and Ludlow (20)). We have been able to collect 4,035 cases, including 46 of our own, in which open operation had been performed. In this group there were 1,908 deaths, a mortality rate of 47.2 per cent. We have also collected 459 cases, including 24 of our own, treated by conservative measures; i.e., closed drainage and the administration of amebicides. There were 32 deaths, a mortality rate of 6.9 per cent. These figures illustrate graphically the advantage of the conservative treatment over the open drainage of amebic liver abscess. In our own series there were 46 patients in which an open operation was done with 9 fatalities, a mortality rate of 19.5 per cent, which indeed compares favorably with the mortality rate obtained from the collected cases in which open operation was done; i.e., 47.2 per cent. There were 24 cases in which the conservative treatment was used with 1 death, a mortality rate of 4.1 per cent. Every case of suspected amebic abscess should be given the advantage of a course of emetine therapy before any other procedure is used unless there is apparently danger of rupture of the abscess. Emetine in 1 grain doses (gm. 0.065) should be given daily for from two to four days before aspiration. Frequently in small abscesses no other therapy will be necessary. In the majority of instances, however, emetine will not suffice and some measure will be necessary to evacuate the abscess contents. After the preliminary emetine treatment aspiration of the liver should be done preferably under local analgesia. Occasionally, however, difficulty is encountered in locating the abscess. A general anesthetic might be used, but is seldom necessary.

Fig. 2. Lateral roentgenogram of chest and diaphragm in amebic abscess of the liver (Case report). Note characteristic elevation of diaphragm and obliteration of costophrenic angle.



chest pain, cough, hemoptysis, or night sweats. No nausea or vomiting. Is constipated; stools dark brown, no blood.

*P. H.*: Dysentery for twelve years, which stopped in 1928; undetermined in type. Eight years ago abscess of undetermined origin in upper right abdominal quadrant which was drained by aspiration but no anti-amebic therapy.

*F. H.*: Father and mother dead, age and cause unknown. Married. Wife and nine children living and in good health.

*S. H.*: Fisherman by trade. Drinks considerable amount of coffee and smokes a great deal. Moderate imbibition of alcoholic beverages.

*P. E.*: Patient is elderly white male, fairly well developed, but poorly nourished. Skin: Warm, moist, elastic, no eruptions or pigmentation. Pulse good, 80 per minute, with slight evidence of sclerosis. Respiration normal. Blood pressure 108/66. Temperature 101.4 degrees F. Right side of chest appears more prominent posteriorly than left, and there is slight lagging on respiration and slight diminution of breath sounds in this area. No rales or friction rubs or tactile fremitus. Liver dullness is slightly higher than normal. On examination of abdomen there is tenderness on palpation over the liver in the upper right quadrant and over the right twelfth rib posteriorly. Liver is enlarged two finger breadths downward. Spleen is not enlarged.

#### Laboratory Examination:

*Urinalysis*: Negative.

*Blood examination*:

|                    |           |
|--------------------|-----------|
| Total R.B.C.       | 4,275,000 |
| Total W.B.C.       | 8,750     |
| Hemoglobin         | 65%       |
| Small mononuclears | 10%       |
| Large mononuclears | 2%        |
| Neutrophils        | 88%       |

*Examination of Feces*: No ova, cysts, or parasites.

*Wassermann*: Negative.

*X-ray examination*: Views of chest show definite elevation of right leaf of diaphragm with obliteration of cardiophrenic angle in AP. view and anterior costophrenic angle in the lateral view (Figs. 1 and 2).

On 9/26/34 thoracentesis was done, and thick, creamy pus obtained, which was sent to the P.D. Report on this was: Smear—No organisms; culture—No growth.

On 10/2/34 consultation with surgery.

Diagnosis: Amebic abscess of the liver. Transfer to Surgical Service.

On 10/4/34 patient was taken to operating room. Under local novocaine analgesia a fairly large aspirating needle was inserted in the anterior axillary line just below the costal margin upward, posteriorly, and medially. A large abscess cavity was entered and 270 cc. of typical chocolate-sauce pus was removed. A smear was made at the time and no motile ameba or evidence of secondary infection found. The specimen sent to the Pathology Department showed no organisms and no growths.

On 10/5/34 patient was given 2 grains emetine hydrochloride; 2 grains on 10/6; 1 grain on 10/7; 1 grain on 10/8; 1 grain on 10/9; 1 grain on 10/10; 1 grain on 10/11; and 1 grain on 10/12/34.

Temperature was 101.4 degrees F. on admission and varied between normal and 100 degrees F. and 101 degrees F. until emetine and aspiration therapy were begun. The following day the temperature rose to 99.4 degrees

F., but after that remained normal until discharged on 10/16/34.

#### SUMMARY AND CONCLUSIONS

1. Amebic infection of the bowel and an associated amebic abscess occur much more frequently than is generally supposed and are not limited to tropical countries.

2. Amebic hepatitis and abscess occur without an antecedent history of diarrhea.

3. Pain and tenderness along the right costal margin accompanied by fever and unexplained liver enlargement are suggestive of amebic hepatitis and abscess.

4. Characteristic x-ray findings are of importance in the diagnosis of amebic abscess of the liver. The aspiration of the chocolate brown sauce pus from the liver is pathognomonic of amebic hepatic abscess.

5. As a large proportion of amebic abscesses of the liver are sterile aspiration of the abscess contents combined with the subcutaneous administration of emetine is the best method of treatment. Open drainage is indicated only in those relatively few cases in which secondary infection of the abscesses occurred. Precaution should always be taken to prevent contamination of uninvolved serous cavities. The prognosis in amebic abscess is good in those cases in which the abscess is sterile and in which closed drainage is used.

6. In a collected series of 459 cases, including 24 of the authors' own, treated by closed drainage the mortality rate was 6.9 per cent as contrasted with a series of 4,035 collected series, including 46 of the authors' own, the mortality rate was 47.2 per cent. In the authors' cases in which open operation was done a mortality rate of 19.5 per cent was obtained, whereas in 24 cases in which conservative treatment was used there was a mortality rate of 4.1 per cent.

7. A typical case of amebic abscess of the liver is reported.

## REFERENCES

1. Rogers, Sir Leonard: Tropical or amebic abscess of the liver and its relationship to amebic dysentery, *Brit. M. J.*, 2:845, 1902.
2. Craig, Charles F.: Amebiasis and amebic dysentery, Springfield, Ills., *Chas. C. Thomas*, 1934.
3. Ochsner, Alton and DeBakey, Michael: In Press. *Am. J. Surg.*
4. Rogers, Sir Leonard: Lettsomian Lectures on amebic liver abscess: Its pathology, prevention, and cure. Lecture I.: Etiology and pathology of amebic liver abscess, *Lancet*, 1:463, 1922.
5. Rogers, Sir Leonard and Megaw, J. W. D.: Tropical Medicine, Philadelphia, *P. Blakiston's Son and Co.*, 1930.
6. Rogers, Sir Leonard: Tropical liver hepatitis and abscess, *Practitioner*, 131:117, 1933.
7. Manson-Bahr, Philip and Willoughby, Hugh: On the leucocyte count in liver abscess, *Tr. Roy. Soc. Trop. Med. and Hyg.*, 22:465, 1929.
8. Granger, Amedee: Radiological signs of subdiaphragmatic abscess, *New Orleans Med. and Surg. J.*, 82:748, 1930.
9. Pancoast, Henry K.: The roentgenological diagnosis of liver abscess with or without subdiaphragmatic abscess. *Am. J. Roentgenol.*, 16:303, 1926.
10. Dickinson, J. C.: Radiographic findings in hepatic abscess, amebic in type, *Radiology*, 4:273, 1925.
11. Love, R. J. McNeill: Amebic abscess of the liver, *Brit. M. J.*, 1:696, 1918.
12. Constantini, H.: De l'ouverture dans le bronches des abces amibiens du foie, *Arch. med.-chir. de l'appar. respir.*, 2:519, 1927.
13. Chen, S. M., van Gorder, S. W., and Yuan, Y. K.: Amebic abscess of liver, *Nat. Med. J. of China*, 17:391, 1931.
14. Manson-Bahr, Philip: Amebic abscess of the liver: Its diagnosis and treatment. A clinical study, *Proc. Roy. Soc. Med.*, (Sect. on Trop. Dis. and Parasitol.), 25:233, 1931.
15. Young, J. R.: A clinical study of liver abscess. Report of 20 cases, *South. Surg.*, 3:79, 1934.
16. Ludlow, A. I.: Liver abscess. Report of 100 cases, *S. G. and O.*, 36:336, 1923.
17. Rogers, Sir Leonard: Lettsomian Lectures, etc. Lecture II: The varieties and treatment of amebic liver abscess, *Lancet*, 1:569, 1922.
18. Chatterji, K. K.: Surgical aspects of amebiasis, *Indian Med. Gaz.*, 57:333, 1922.
19. Manson-Bahr, Philip; Low, George C.; Pratt, J. J., and Gregg, A. L.: The treatment of liver abscess by aspiration with account of 15 cases, *Lancet*, 1:941, 1923.
20. Thurston, E. O.: Liver abscess, series of 64 cases, *Lancet*, 207:1008, 1924.
21. Ludlow, A. I.: Treatment of abscess of the liver by aspiration and subcutaneous injection of emetine, *China Med. J.*, 38:93, 1924.
22. Kilner, T. P.: Operative procedures in amebic abscess of the liver based on recent experiences, *Proc. Roy. Soc. Med.*, (Sect. on Trop. Dis. and Parasitol.), 25:242, 1931.
23. Talbot, Philip: Fifteen cases of liver abscess, *Brit. M. J.*, 2:375, 1919.
24. Chatterji, K. K.: Non-suppurative and suppurative hepatitis and splenitis of amebic origin, *Indian J. Med.*, 1:259, 1920-21.
25. Leake, Chauncey D.: Personal communication.
26. Rinehart, James F., and Anderson, Hamilton H.: Effect of emetine on cardiac muscle, *Arch. of Path.*, 11:546, 1931.
27. Leake, Chauncey D.: Chemotherapy of amebiasis, *J. A. M. A.*, 98:195, 1932.

## ABSTRACTS

THOMAS M. JOYCE, M.D.

*Tumors of the Small Intestines, Annals of Surgery.*  
Vol. 100, Nov., 1934, No. 5.

Dr. Joyce calls attention to the fact that relatively few tumors of the small intestines are diagnosed before operation. Raiford in a review of a series of 88 small intestinal tumors found the incidence of malignancy to be 43 per cent.

Carcinoma of the small bowel is usually of the annular type with a tendency to constriction, readily adherent to adjacent structures. On malignant degeneration of a small papilloma such a growth is quite massive yet causes no obstruction of the small bowel.

The benign growths are usually intraluminal, freely movable, non-adherent externally, with a tendency to intussusception.

The most common location for carcinoma of the small bowel is the duodenum and then the jejunum. The ileum shows the lowest incidence of carcinoma and the highest incidence of tumors of the lymphoblastoma group.

Many so-called lymphoblastomas eventually turn out to be on a chronic inflammatory basis. The majority of benign tumors are adenomata and may occur in any place in the small bowel—the greatest frequency is the ileum, next duodenum and last in the jejunum.

**SYMPTOMS:** 1. The picture is generally that of an obstruction—usually a partial intermittent affair. Except in intussusception do we have the picture of complete obstruction. Intussusception is a complication of about 30 per cent of all small intestinal tumors.

2. Hemorrhage, either gross or microscopic.

3. Pain due to obstruction present.

4. The presence of a mass palpable at any time, probably the most important physical sign to be looked for. It may not be constant as in intermittent intussusception. One important characteristic is their mobility.

The presence of unexplained gastro-intestinal hemorrhage, intermittent obstruction or a history not typical of any other common abdominal condition should draw attention to the possibility of a tumor of the small intestines.

The x-ray examination is of great importance in establishing the pre-operative diagnosis of these lesions, especially in showing distended loops of small bowel evidencing obstruction.

Charles T. Sturgeon, M.D., Los Angeles.

STANTON, E. MACD.

*Acute Appendicitis. S., G., and O.*, 59:738, 1934.  
1934.

The author reports a series of 1004 cases of acute appendicitis, covering the period from 1907 to 1934. Analysis of these cases emphasizes two fundamental truths:

1st: The operative mortality of acute appendicitis bears a definite relationship to the acute inflammatory processes prior to the time of operation. For practical purposes the duration can be measured in terms of the day of the disease on which the patient is operated upon. Mortality after operations, during the first 24 hours of the attack, is about 1 per cent. Average mortality during the second day of attack is from 2 to 3 per cent. After about 40 hours, the rate tends to rise sharply, so that in cases in which the operation is done on the third day of the attack, the operative mortality averages about 10 per cent. Fourth or fifth day operations are even more dangerous than third day operations. Beginning with the sixth day, operative mortality starts to decline, and by the ninth or tenth day it again corresponds approximately with second day cases.

2nd: Mortality rate is observed from day to day in this disease is inseparably associated with the corresponding sequence of changes in the inflammatory process itself, in both the appendicitis and the complicating peritoneal lesion. By the third day the intra-peritoneal exudate is of a distinctly purulent character. There is, as yet, little or no evidence of the formation of sharply defined abscess cavities. Patient has not developed any considerable immunity to the infection. By the sixth day, definitely defined abscess cavity begins to be formed with development of relative immunity against the infection.

K. Hosoi, New Orleans.

COLLER, F. A., AND POTTER, E. B.

*The Treatment of Peritonitis Associated With Appendicitis. J. A. M. A. 103:1753 (Dec. 9), 1934.*

This paper deals with a study of 336 patients with acute appendicitis. There were 213 cases in which the disease was limited to the appendix or its immediate vicinity. There was only one death in this group, a mortality rate of 0.46 per cent. The second group consisted of eighty-five patients. In these patients the diagnosis of a diffusing peritonitis was made. Eight patients of this group died giving a mortality rate of 9.4 per cent.

The third group comprised thirty-five patients. A definite diagnosis of appendiceal abscess could be made in all of these cases. Two patients died in this group, a mortality rate of 5.7 per cent.

A fourth group of three children admitted to the hospital in a moribund state are included in the mortality statistics of the entire study.

It is with the group of eighty-five patients whom the authors are particularly interested. They emphasize that the diagnosis of a diffusing peritonitis is not easy. They stress the Hippocratic "facies," dehydration from vomiting fever often up to 104F, rapid pulse and respiration rates, restlessness and a rigid diffusely tender abdomen and a high leucocytosis. The treatment they have used in this group consists of Fowler's position, heat to the abdomen, and morphine in sufficient quantities to keep the patient free from pain and apprehension. The stomach is emptied by siphonage. Nothing is given by mouth. Physiologic solution of sodium chloride and 5 per cent dextrose solution are given alternately by continuous intravenous drip, at least 5000 cc. is given daily to an adult. The urine and blood chemistry are studied. No enemas are given.

The authors feel that this deferred operation method of treating cases of appendicitis with diffusing peritonitis is of definite value.

Francis D. Murphy, Milwaukee, Wis.

GILE, JOHN F., AND BOWLER, JOHN P.

*The Management of Perforated Appendicitis. J. A. M. A. 103:1750 (Dec. 8), 1934.*

The authors present a series of 901 cases of appendicitis. The discussion is concerned with the handling of cases of perforated appendicitis which they classify into three types, group one, gangrenous appendicitis with local peritonitis; group two, appendiceal abscess; and group three, perforation with general peritonitis.

The authors are convinced that immediate operation in early peritonitis has prevented the development of diffuse peritonitis in some of these cases. They feel that appendiceal abscess represents a localized process from the very start and presents no emergency needs. They stress that late general peritonitis involves an enormous mortality.

They emphasize early observation, early diagnosis, and early operation.

Francis D. Murphy, Milwaukee, Wis.

DIXON, CLYDE F.

*Carcinoma of the Cecum: What Are the Chances for Cure? J. A. M. A., 103:1605 (November 24, 1931).*

The author reviews one hundred and forty-five patients of cancer of the cecum where resection was performed. Of these one hundred and forty-five patients, sixty have lived for five years or longer following resection. The outstanding features in regard to these sixty cases were: the patients had lost weight markedly; they had a secondary anemia; and a mass could be palpated in the right lower abdominal quadrant. Obstruction is a variable symptom in cases of carcinoma of the cecum.

The duration of the symptoms varied from a few weeks to many years.

Involvement of the lymph nodes was found in fifteen of the sixty cases. The posterior wall of the cecum was the most common site of the malignant growths.

The surgical treatment of carcinoma of the cecum consists of radical removal. Some surgeons perform the operation in one stage, others prefer to do an ileocolostomy. If the patient's condition is good, a one stage resection may be done. Anastomosis has to be performed between the ileum and the transverse colon.

The preparation of patients for operation is very important. They are given a diet of 2,800 calories a day, of foods of lowest residue, principally carbohydrates, such as fruit juices, candies, custards, gelatin, rice, eggs, thin soups and broths.

Francis D. Murphy, Milwaukee, Wis.

R. E. CHURCH AND J. W. HINTON.

*A Study of 671 cases of peptic ulcer with special emphasis on 114 post-operated cases. N. Y. State Journ. of Medicine, 34:24, 1079 to 11084, Dec. 15, 1934.*

From the Gastro-Enterological Clinic of the Fourth Medical and Surgical Divisions at Bellevue Hospital, Church and Hinton report 671 cases of peptic ulcer in six years. Of these 164 had already been operated upon. Of the remaining 507 surgery was found necessary in 46. Before considering surgery each patient was submitted to a strict medical regime. Perforation and severe hemorrhage each occurred fifteen times. By patient persistence with the medical treatment, the authors find that very few ulcers cause organic obstruction, and that the real indication for operation is severe pain unrelieved by medication or diet. The cause of such pain is probably pancreatic.

The authors have reviewed 114 operations in 103 chronic ulcer patients, excluding 81 cases of perforation. There were 92 males and 9 females, 78 of them being between the ages of 20 and 50, and four above 60. Of occupation the largest group, 14, were chauffeurs, truckmen and automobile mechanics, while 13 were clerks, ticket agents, cashiers and teachers and 6 were housewives.

The answers to the question: Why was the patient subjected to surgery? were: (1) Uncontrollable pain in 85, (2) Obstruction associated with pain in 10, (3) Bleeding associated with pain in 8, (4) Obstruction alone in 4, and (5) Obstruction with bleeding in one. There were 85 gastroenterostomies, 11 resections, 7 pyloroplasties, 5 simple excisions and 3 dissociations of old gastroenterostomies. Eleven of the series had preoperative hemorrhage and 12 postoperative hemorrhage.

Following 96 short-circuiting operations, there were 16 marginal ulcers, or 16.7 per cent. These operations were all done in the vicinity of New York City and no one surgeon performed any two operations. The marginal ulcer cases followed to a great extent the same course as an original ulcer case and were treated by the same medical regime. Operation was done only when pain could not be relieved. The end results in 106 surgical cases were 39 cured, 13 benefited and 55 unimproved. Of the last group sixteen have developed marginal ulcers. Thirteen patients who obtained complete relief from their symptoms through operation, eventually had severe recurrences, six of them over five years after operation, and one twelve years after operation. The authors conclude that present methods of treatment, whether medical or surgical, do not give a hopeful outlook for ulcer patients.

Walter A. Bastedo, New York City, N. Y.



## SECTION VII—*Surgery of the Lower Colon and Rectum*

### Pruritis Ani—A New Treatment

By

NATHAN J. SIMMONS, M.D.  
BOSTON, MASSACHUSETTS

**P**RURITIS ani is one of the most troublesome affections encountered in rectal surgery. It is characterized by persistent intense itching in the anogluteal region. Physicians often belittle the manifestation and dismiss the patient with a smile and a salve.

Gant (1) has listed over one hundred causative factors. The methods of combatting this condition are probably twice as long.

The first and frequently only point on which there is any general agreement in respect to the problem of treating pruritis ani is this: Try to remove the cause.

The only pathologic changes seen on examination may be pleats and folds in the perianal skin. There are two varieties, the dry and the moist. The first is characterized by a thickened, indurated skin, while the second presents an excoriated and macerated appearance with bleeding points.

My classification as to the etiology of pruritis ani is:

I. Pathological changes in or about the rectum and anus, such as colitis, proctitis, fissures, fistulae, hemorrhoids, cryptitis and papillitis, ulcers, skin tags, tumors of the rectum, and mucous polyps.

Montague (2) in 349 cases reported that 67% of local rectal pathology was the causative factor of pruritis ani. Frequently colitis or proctitis are the underlying causes.

Jameson, (3) Albright, (4), and Decker (5) describe red lines seen in some cases under the perianal skin which, they maintain, are channels draining an acid secretion from an inflamed mucosa and irritating the skin. These cases might respond to the treatment of repeated injections into the mucosa of quinine-uria hydrochloride (5%) or phenol in oil (10%). The solution causes an inflammatory fibrosis and seals off the channels from the discharge. Irrigation of the rectum and regulation of the diet may help to allay the inflammation of the mucosa. Fissures and fistulae by their irritating discharges may also incite itching and, therefore, should be eradicated.

Internal hemorrhoids, although they are not the greatest cause of pruritis ani, should be removed or treated by the injection method when present.

II. Infections of the skin or mucous membrane

a. Bacterial infections

Murry (6) took cultures from the itching areas and found that the streptococcus fecalis was quite predominant. A vaccine was made up of this material, and 168 patients were treated with only 13 failures.

Twelve to twenty injections were given to each patient. One hundred seventy-five million to one billion killed organisms were given at each dose.

Knowles (7) and Carson (8) also reported good results with this treatment but occasionally had to add the colon bacilli. The vaccine supposedly was given to raise the opsonic index which is said to be below normal in these cases. Non-specific therapy may be responsible for the relief of the itching rather than the specific form of therapy.

Montague (2) on his own investigation found the staphylococcus albus and colon bacillus where the epidermis was injured by traumatization or maceration. He treated a few cases by injection of a vaccine made of this culture but obtained poor results.

Bassler (9) and Connors (10) used an autogenous vaccine twice a week made of streptococcus fecalis, and gradually increased the dosage until reaction was obtained. They reported very favorable results. The injections were given subcutaneously.

b. Fungi and mycotic organisms

The epidermophyton, trichophyton, yeast, and molds have been recovered from scrapings taken from the itching perianal skin. Tests were performed by soaking the scraped scales in 25% potassium hydroxide and examining them under the microscope. These organisms cause some skin changes. Treatment should consist of a suitable fungicide.

c. Scabies and pediculosis

These two conditions are apt to go undiscovered when not thought of.

d. Trichomonas vaginalis may cause intense itching about the anus. It is wise to examine, and if present, treat that condition by carbasone suppositories, Lassar's paste, or sodium perborate douches. A heavy leukorrhea may cause sufficient irritation to start the patient scratching, cause infection, and beginning of a pruritis ani. It can be corrected by proper attention.

III. Systemic diseases causing peri-rectal itching

a. Diabetes

b. Liver disease

c. Anemia, exophthalmic goiter, menopause, pregnancy

d. Worms, especially pin worms in children

e. Genito-urinary diseases, causing itching reflexly

f. Food allergy—sensitization

g. Syphilis

h. Neurosis



#### IV. Idiopathic or Essential pruritis ani

We must eliminate all known causes before we are justified in classifying a case as essential or idiopathic. It is in this group that treatment of various sorts have been particularly numerous. Treatment in this group is divided into the following: Hygienic, dietetic, and local.

The physician must stress cleanliness of the anal region particularly after defecation. The parts about the anus often respond to a lysol washing 1:80. The success of this treatment speaks for a non-specific infection. The patient must be cautioned against scratching and infecting himself. Night covering should be light and warm. Wool blankets should not be next to the patient. Keep the sleeping room at a cool temperature. A good quality cleansing tissue or toilet tissue should be used. Frequent bathing and thorough drying with an application of dusting powder will allay the irritation.

The diet should consist of bland foods. Avoid hot, rich, or sweet foods, and condiments. Care should be taken that neither constipation nor a fluid bowel movement occur.

Local treatment consists largely of local subcutaneous injections of anesthetics or alcohol and applications of antiseptics. A great variety of preparations have been used.

Hopfinger (11) treated 11 stubborn cases of pruritis with diathermy. He reports 8 cures, 2 partial cures, and 1 failure. Contraindications to this treatment are eczematous or pyogenic lesions in the skin.

I have injected  $\frac{1}{4}$  to  $\frac{1}{2}\%$  of quinine-urea hydrochloride subcutaneously about the itching area. As much as 20 to 40 c.c. may be used at one time, but the injection causes a great deal of pain. I preceded it by  $\frac{1}{2}$  to 1% procaine solution to ease this pain. Anesthesia is obtained for about two to four weeks.

Hanes (12) advocates subcutaneous injections of dilute hydrochloric acid in 1:5000 or 1:2000 preceded by 15 to 30 c.c. of  $\frac{1}{2}\%$  novocaine solution perianally or morphine sulphate subcutaneously for pain. Fifteen to twenty c.c. of the dilute hydrochloric acid are injected and repeated at weekly intervals for about four treatments. His theory is that the acid kills the organism or causes its environment to be uninhabitable. It does not destroy the nerve endings. It causes an influx of blood to the drained tissues. Leukocytes are increased. Hospitalization for one-half to one day is best for patients who undergo this treatment.

Stone (13) uses 95% grain alcohol. It is painful if not preceded by novocaine. He measures off squares one-fourth of an inch apart about the anus, plunges a very fine needle through the skin into the subcutaneous tissue, and deposits two to four drops in each square. He reports excellent results. Itching is abolished at once; numbness develops just as in an operative procedure. Injections are repeated as often as one desires. Anesthesia and relief from pruritis may persist for six months to a year. His cases must have at least eight to ten treatments.

Buie (14) hospitalizes his cases and injects 20 to 40 c.c. of alcohol subcutaneously at one time. Sloughs appear quite frequently but heal in time.

Goldbacker (15) uses 5% phenol in oil and injects it subcutaneously about the itching area.

Gabriel (16) uses a solution called A. B. A., a mixture of anesthine (5%), benzyl-alcohol (10%), and

phenol (1%) in 5 c.c. of sterile oil and obtains very favorable results. I have used this, but I find that it causes a great deal of pain. Anesthesia is prolonged three to six months in some cases.

Ycoman (17) and his associates use benacol solution. It is only slightly anesthetic to the peripheral nerve endings. Anesthesia lasts for about two weeks.

Tashjian (18) has been able to mobilize histiocytes about itching areas by injections of sterile broth solution, triple distilled water, or hemoglobin. He claims these histiocytes have phagocytic tendency and destroy the prevailing infection. The nutrient broth consists of 3 gms. of meat extract, 10 gms. of peptone, and 8 gms. of sodium chloride adjusted to pH 7. Thirty c.c. are injected subcutaneously at one time. All wrinkles are smoothed out, and this is repeated every three days for four consecutive treatments. A rest period of two weeks is given and then the same course of treatment is repeated. He states that he has obtained clinical cures over a long period.

Rolfe (19) employs ionization with antiseptics. Theoretically, it should prove of value, but I have not observed permanent or long relief from this method, relief being obtained only while treatment is being given.

X-ray is a painless procedure, but I think it is much overrated, and itching is worse if it fails. Pruitt (20) claims fifteen to twenty cures.

Surgery, the undercutting operation, is resorted to when corrective measures by all these methods offer no relief. The patient requires hospitalization, and the pruritis may return in six months to one year. Flynn (21) claims ten cures after two to five years in twelve patients.

Gabriel (16) has had the Ciba Company make up a solution from a new formula which offers painlessness of injection and prolonged anesthesia. It is a solution of nupercaine (0.5%), phenol (1%), and benzyl-alcohol (10%) in almond oil.

It has not been placed on the market, but the Ciba Company has supplied me with ampules for experimental purposes on my private patients. I have used this solution with excellent results in 20 cases, freedom from pruritis lasting four to six months.

After cleansing the anal region 5 c.c. of this solution are injected under the itching area. I inject the posterior quadrant on the first visit and the lateral and anterior quadrants on subsequent visits. Pooling of the oily solution, infection, or eczema may lead to sloughing and a prolonged healing period.

For illustration two case records are presented.

Case I. O. D., age 23, a shipper, complained of considerable pruritis ani for two years. Procto-sigmoidoscopic and anoscope examinations were negative for pathological changes. The perianal skin was thickened, and there were many skin folds. Numerous bleeding points from scratching were seen. Injection of 5 c.c. was made subcutaneously in posterior quadrant on June 8 with repeated injections on June 15, June 22, and June 27, taking in entire perianal region. Patient reported appreciable relief after the first injection and entire disappearance of symptoms after the fourth injection. Four months check-up finds the patient without symptoms.

Case II. W. G., female student, age 29, complained of perianal itching of nine months duration. Sigmoidoscopic and anoscope examinations were negative. The skin was moist with bleeding points. Three injections were given with complete disappearance of symptoms for six months.

## SUMMARY

The possible causes of pruritis ani are many and their detection quite difficult. Every patient must be studied carefully and properly classified in order to relieve the underlying condition.

Many ways of combatting this condition have been enumerated.

A new solution with method of injection has been described. Twenty cases have been injected with this solution resulting in freedom from symptoms from four to six months to date.

## REFERENCES

1. Gant: *Diseases of the Rectum and Colon*. (Saunders)
2. Montague, J. F.: *M. J. and Rec.*, 130:63-65 (July 17) 1929; *Arch. Dermat. and Syph.*, 10:42-55 (July) 1934.
3. Jameson, A. B.: *M. J. and Rec.*, 129:496-497 (May 1) 1929.
4. Albright, J. D.: *M. J. and Rec.*, 129:496-497 (May 1) 1929.
5. Decker, J. B.: *M. J. and Rec.*, 132:553-554 (Dec. 3) 1930.
6. Murry, cited by Gabriel, W. B.: (Reference 16).
7. Knowles, F. C.: *Arch. Dermat. and Syph.*, 7:505-509 (April) 1923.
8. Carson, E.: *Arch. Dermat. and Syph.*, 7:505-509 (April) 1923.
9. Bassler, A.: *M. J. and Rec.*, (September) 1933.
10. Connors, R. J.: *M. J. and Rec.*, (September 6) 1933.
11. Hopfinger: *Wiener Klinische Wochenschrift*, Vienna, Vol. I, No. 8 (August 25) 1928.
12. Hanes, G. S.: *Trans. South Surg. Assoc.*, 40:53-156, 1927.
13. Stone, H. B.: *Surg., Gyn., Obs.*, 42:565-566 (April) 1926.
14. Buie, L. A.: *Mayo Clinic Monograph*.
15. Goldbacker, L.: *A. M.*, Vol. 35 (May) 1929.
16. Gabriel, W. B.: *British M. J.*, 2:311-312 (August 30) 1930.
17. Yeoman: *Proctology*. (Appleton)
18. Tashjian, S. H.: *Northwest M. J.* (March) 1933.
19. Rolfe, cited by Oliver, E. L., and Lyons, M.: (References 22, 23).
20. Pruitt, M. C.: *J. Med. Assoc. Georgia*, 21:43-49 (February) 1932.
21. Flynn, C. W.: *Trans. South Surg. Assoc.*, 42:256-258, 1927.
22. Oliver, E. L.: *Arch. Dermat. and Syph.*, 14:560-565 (November) 1926.
23. Lyons, M.: *Amer. J. Elec. and Rad.*, 43:139-143 (April) 1925.
24. Hayes, H. T.: *Southern M. J.*, 24:39-311 (April) 1931.

## OBITUARY

## Dr. Lewis Stephan Pilcher

DR. Lewis Stephen Pilcher, scholar and editor for half a century of the oldest surgical journal in the United States, the *Annals of Surgery*, died this morning at eighty-nine years of age. Country school teacher, country practitioner, naval surgeon, student of tropical disease, anatomist, professor of surgery, editor, bibliophile, patriot—these nouns indicate a few of his many interests and activities over a long and intensely useful life.

Lewis Stephen Pilcher entered the University of Michigan at the age of thirteen, and took his bachelor's degree at seventeen, the youngest matriculant and the youngest graduate of that great institution. His master's degree was added within a year; and in that same year he entered upon medical study. This was in 1863 when the Civil War was raging. The next year found him with enough medical knowledge to volunteer as a hospital steward and throw himself into the thick of service to the sick and wounded. Then back to the University of Michigan and the doctor's degree in 1866. Many years later, 1900, this same institution conferred upon him the honorary degree of Doctor of Laws. Practice began in a rural district of Michigan at the age of twenty; at the same time, to guarantee a livelihood, teaching in the little schoolhouse by the blacksmith shop. He rode his horse across the countryside to the call of the sick, followed the current literature of medicine, and for diversion

read the classics in their original Greek and Latin.

The next move was to an internship in a Detroit Hospital. Then a post-graduate course in the hospitals of New York City. And then came the successful examination and appointment as Assistant Surgeon in the United States Navy, in 1867. His marriage, retirement from the Navy, and entrance into private practice, in 1872, all spelled romance and adventure. Then came the years of practice. But Pilcher wanted something more. He organized a dissecting room in his house. This expanded into an adjacent building. A museum and library grew up in connection with it. He dissected also at the Long Island College, and became Adjunct Professor of Anatomy, in 1879, and Surgeon to the Dispensary. In 1885 he was appointed Professor of Surgery at the New York Post Graduate Medical School.

In 1884 he became editor of the *Annals of Surgery*, which position he has occupied to the present day. This publication, beginning in 1884, was acquired in 1897, by J. B. Lippincott Company. The editorial policy and censorship of advertising have never been relinquished by the Editor. If we add to the fifty years of the *Annals of Surgery*, the seven years of the *Annals of Anatomy and Surgery*, and its predecessor which he inspired and dominated, this period of medical editorship establishes him as the dean of medical editors in the United States, if not in the world.

## SECTION VIII—*Editorial*

*The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Association is in no way responsible for editorial expressions.*

### GENERAL PRINCIPLES INVOLVED IN THE DIAGNOSIS OF GASTRO-INTESTINAL DISEASE

**A**CCURATE diagnosis in the field of gastro-intestinal disease is still a very difficult matter notwithstanding the tremendous amount of work of high character which has long been devoted to this field. Gastro-intestinal disease is one of the oldest recognized and best defined of the medical specialties. The subject of the physiology of the gastro-intestinal tract has been also one of the earliest and most intensively studied of the special systems. The field of gastro-intestinal disease always has been and still is one of the most attractive and important of the whole subject of internal medicine. The subject has never been relatively a neglected one nor has it ever failed to comprise among its workers many of the greatest of medical minds of the period for many generations past.

Dietary laws and rules have characterized almost every primitive as well as all civilized peoples, and yet we must honestly class as but little better than taboos and prejudices many of the dietary customs of the present day. Religion and racial custom still determine the so-called laws of dietetics far more certainly than do the results of scientific research and study.

The fact of the difficulty still existing in the diagnosis of gastro-intestinal disease is not the result of lack of facilities and opportunity offered by scientific progress and study. Mechanics and physics early contributed their methods to the study of the gastro-intestinal tract and a relatively correct interpretation of the primitive functions of the tube very promptly was recognized by all of the early anatomists. The Zapotecs and the Mayas among others, of our own hemisphere probably understood the anatomy of the tract very early, certainly long before the brake-like incubus of religion permitted adequate anatomical studies of the human body in Europe and perhaps even in Asia.

Long before chemistry had risen to the dignity of a science its methods of study were being applied also to the elucidation of gastro-intestinal problems, and this science in particular still remains one of the most fertile fields of study in connection with the subject. Experimental physiology almost may be said to have had its conception in studies of this field and it remains even to this day one of the most valuable methods of study, present and future.

The discovery of the microscope almost immediately contributed its help in direct application to the study of the physiology and pathology of the digestive tract, and at least in diagnosis we but stand on the threshold of its possible contributions to the subject.

Radiology, as you shall hear later, has become one of our most effective arms in the conquest of gastro-intestinal disease, and yet our errors in the diagnosis of disturbances of the gastro-intestinal tract are of shocking frequency, and our knowledge of selective dietetics still rates below that of the instinct of the lower animals. As a matter of fact our dietetic habits are still more dictated by instinct, custom and ancestry, sometimes even by religion, than by scientific fact.

I am fully aware that my statements must seem to many of you who have considered the matter, as very broad and rash. Especially must they seem so to those of our cloth who have devoted their chief interests to this field throughout long and rich professional lives.

I believe however that a dispassionate weighing of the facts of diagnostic error in this field as shown in the dead house of any large general hospital will serve to substantiate my statements in general. The timeliness of such a period of intensive study as we are inaugurating tonight will no doubt be apparent to us all before the days of the period of this serious consideration are over.

There are of course reasons for our particular frailties and inadequacies in this field of diagnosis. I think it will be helpful, if not flattering, for us to consider a few of them. Many, if not most, of our failures are due to the extreme complexity of the subject and to the delicate integration which the gastro-intestinal tract bears to all the other functions of the human body both in health and in disease.

We may almost correctly state that there are no general or special disturbances of the body which do not manifest themselves in some degree at least by symptoms or signs of gastro-intestinal disorder. Consider for example the very familiar symptom of nausea. It appears as an evidence of fright, of worry, and of many if not most other forms of mental and nervous disease. It is developed by vertigo; it is a sign of pregnancy; it is one of the initial symptoms of most of the infections; it is intimately associated with visual disturbances, with trauma, shock, malnutrition, and with most of the surgical as well as medical diseases of the abdomen. It is frequent in pneumonia and in trauma of the thorax, even with those of the extremities. I believe that one may almost say that it is the most frequent symptom of all diseases of the body and of many physiological variations. It is even occasioned by political conditions, particularly at the present time. This is but an example.

The welfare of the entire body is essentially dependent on the integrity of the gastro-intestinal tract. Most disease conditions of any of the systems, cause not only symptoms but abnormal signs also of the gastro-intestinal tract. Worry and fright check or limit gastro-intestinal secretion, favor abnormal putrefaction and fermentation, delay or paralyze the all-

Opening address.

\*Read before the Fortnight. Session of 1934, New York Academy of Medicine, Oct. 21, 1934.

†Attending Physician to Bellevue Hospital, Fourth Serv...  
Submitted October 24, 1934.

essential peristalsis, manifested by chemical and radiographic signs familiar to us all. Innumerable other states and diseases far remote anatomically from the gastro-intestinal tube also wreck changes of the same character.

Gastro-intestinal symptoms, signs and pathology are among the most constant evidences of cardio-vascular disease and even the properly trained cardiologist must know how to distinguish these symptoms; he also must be a gastro-enterologist. The student of renal disease constantly is called upon to differentiate gastro-intestinal signs and symptoms due to kidney defects from those produced by integral pathology of the gastro-intestinal tract or perhaps from identical findings and symptoms primarily caused by widely distant and entirely foreign pathology to that of the organs in which he is primarily most concerned.

Genital and endocrine diseases cause marked vagaries of the functions and signs of the digestive tube. Even the endocrinologist and the obstetrician must be serious students of gastro-enterology. This is equally true of every speciality of medicine. The student of dietetics in particular must familiarize himself with the ethnology, the history and the sociology of gastro-enterology. Woe betide the patient of the specialist in pulmonary disease whose attendant never explores below the costal margins.

I think that I have presented sufficient excuse for the tremendous difficulties of accurate diagnosis in gastro-intestinal disease, and incidentally I trust I have pointed out the great need which every practitioner and every research worker has for a broad general knowledge at least of the general principles concerned in the diagnosis of gastro-intestinal disturbances.

It is of course axiomatic, for the same reasons that the specialist in the diagnosis as well as the therapeutics of the gastro-intestinal tract must be most broadly informed on general diseases and especially concerning those conditions such for example as pernicious anemia, sprue and the like which are strikingly evidenced by gastro-intestinal signs and symptoms.

The gastroenterologist who is not an earnest student of internal medicine in particular is a very poor gastroenterologist. I say this in no disparagement of the gastroenterological specialist or for that matter of any other specialist, for true specialization in this day and stage of medical evolution is indispensable, and especially so in the tremendous field of gastroenterological diagnosis which demands not only broad learning but also very high technical training and ability in the very difficult and highly intricate methods of this speciality. Concerning this you will hear very much from far greater authority within the next few days. My purpose is to point out as convincingly as possible the absolute need for breadth of vision on the part of every one of us and at the same for as high a degree of technical perfection in the methods of diagnosis as is possible for any of us to attain. Even with such equipment, error in this difficult field is certain to occur all too frequently with the very best of us, and it is our hope that the frank discussion, earnest study and broad demonstrations which we are to receive within the next few days will return all of us to our offices and clinics better prepared to recognize and to treat the patient suffering from gastro-intestinal symptoms and pathology.

It is not my function this evening to enter into the technical details of the diagnosis of gastro-intestinal diseases but rather to point out the general principles which apply to them. In extension of the ideas presented above, I would then first state that in every case of suspected gastro-intestinal disease a preliminary general examination should be made so that gastro-intestinal disorders of extra visceral origin may be first detected. This should eliminate from confusion such conditions as reflex vomiting, pernicious anemia, sprue, cerebral disease and many other conditions in which treatment should be directed primarily to pathology outside the gastro-intestinal tract.

I feel also that second consideration should be accorded to the possibility of gastro-intestinal signs and symptoms developing as a result of disease factors introduced entirely from without. Such infections as uncinariasis for example, and other similar conditions may be readily enough confused with instances of gastric carcinoma or ulcer as they are in no small number of cases. Inadequate, superabundant, unbalanced or unaccustomed diet must be also considered as responsible for many signs and symptoms of gastro-intestinal disease and one must recall these possibilities before assuming primary pathology of the tract itself.

In relation to these dietetic problems as a cause of gastro-intestinal disease it must be recognized that racial and ancestral customs play a very important part particularly when radical changes in physical habits, in climate, altitude and in sun and light conditions exist. Roughly stated, it will be found as a general rule that the most desirable diet and dietary customs in any locality will be those which the natives in that area habitually select.

As has already been stated, it is not the function of this paper to consider in and detail the special technic of diagnostic examinations since all these are to be taken up in detail both in lecture and in demonstration. There are however certain general points in the diagnosis which properly fall to my function for presentation.

The first of these is to point out that in diagnosis as in treatment, the gastro-intestinal tract can not be considered as separated from the general organism. On the contrary it is only when the general condition of the body as a whole is fully appraised that we are able properly to evaluate the data which lead up to adequate diagnosis; hence I feel that final diagnosis can only be arrived at properly after a general examination of the entire body has been conducted and weighed in relation to the evidence of history and environmental conditions. This must be then supplemented by a careful special examination of the gastro-intestinal tract by whatever special technic may be indicated by the evidence elicited.

In the course of this seminar you will be appraised fully of all of the newer methods of examination and of the invaluable data which they are able to present to the diagnostician. You will in particular be authoritatively informed of the tremendous contributions of radiography to this special field of medicine.

In regard to the radiographic findings in particular I wish however to sound a warning note. So accurate, so valuable has the roentgenographic measures for the diagnosis of gastro-intestinal pathology become that many clinicians, especially some of the younger school

have, I feel, come to rely too exclusively either in a positive or in a negative way on X-ray findings in diagnosis. Too often in the work-up of average hospital cases of gastro-intestinal disease I find that the X-ray findings only are sought, with an almost complete ignoring of the tremendously valuable lessons which chemical examinations of the secretions are still capable of furnishing us. Too often the intern resorts to the use of the fluoroscope and X-ray plate before, rather than after, a proper history has been taken. Chemical and microscopic examinations are neglected or undervalued in the face of positive or negative radiographic facts, and by no means infrequently, grave errors in diagnosis and in treatment therefore ensue. New methods have much supplemented, but rarely displaced the old.

Quite as often also do we find that the physical examination has been slighted or even omitted. Too frequently because of negative X-ray findings, the rectoscope and sigmoidoscope and their great possibilities in the way of accurate diagnosis are forgotten. Too often, far too frequently, even is the simple procedure of a digital examination and inspection of the anus and rectum omitted under the excuse that the X-ray findings are reported as negative.

These errors of neglect are not the fault of the radiographer; they are even very commonly the result of his too great efficiency in the diagnosis of gastro-intestinal pathology so that the other methods of examination are neglected. I also feel that recognizing as we must the high technical skill of the average modern radiographer, that the clinical diagnostician neglects to view himself the films assembled by the expert, as it were, through the eyes of the clinician, and too often also does the clinician forget the tremendous value which may be afforded him by his own use of the fluoroscope, again viewed thru the eyes of the clinician, familiar as he should be with the chemical, microscopic and physical aspects of the case, all thrown as it were, on the screen of that most valuable of all diagnostic methods, a well and personally taken history.

Finally I would again impress upon all of you the very great variations which occur in the gastro-intestinal tract still within the wide range of physiological idiosyncrasy—very frequently these almost imperceptibly verge over the line into real morphological or chemical pathology, while yet still capable of correction along physiological methods of treatment.

The gastro-enterologist must be a very broad man, one familiar with many fields within the realm of medicine and yet superficially viewed as far from the definite subject of gastro-intestinal disease. Not for one moment may he be allowed to forget that gastro-intestinal physiology and pathology are inextricably blended with the functions of the body as a whole and as a result of its reactions to environment.

Harlow Brooks, New York City, New York.

#### ENTEROGASTRONE

**T**HE original observation of Ewald and Boas (1886) that the presence of undigested fat in the upper intestine causes an inhibition of gastric motor activity has been repeatedly confirmed. That fat has a similar inhibitory effect on gastric secretion was demonstrated by Pavlov and his students (Labassov). The nature of the inhibitory mechanism concerned has

been considered to be entirely nervous until recently.

In 1926 Farrell and Ivy (1) introduced a new concept concerning the mechanism of the inhibition when they observed inhibition of an auto-transplanted gastric pouch following the introduction of fat into the main stomach. This demonstrated that a humoral agency must be considered as playing a rôle in the gastric inhibition caused by fat. This was soon confirmed by Lim and his colleagues (2). Later, Feng, Hon and Lim (3) found that fat also inhibited the secretion of a transplanted gastric pouch, and that the inhibitory humoral agent was not some post-absorptive circulating substance originating from digested fat. Quigley, Zetteman and Ivy (4) similarly found the inhibition of motility caused by fat was not due to post-absorptive circulating fatty substances.

Quigley and Rneips (5) have recently submitted evidence showing that glucose acting in the upper intestine inhibits gastric motility by some humoral agency and that the agent was not the absorbed circulating glucose.

These observations, of course, suggested the possibility that when undigested fat (fatty digests stimulate secretion and motility) contacts the upper intestinal mucosa a chalone (inhibitory autacoid) is elaborated and carried by the blood (fatty lymph is inactive) to the stomach where it causes inhibition of motility and secretion. If this hypothesis were true such an inhibitory substance should be extractable from the upper intestinal mucosa.

In fact, Kosaka and Lim (6) have found that when relatively large doses of a cholecystokinin preparation, supplied by the author, were injected intravenously gastric secretion was inhibited. This stimulated Lim and his colleagues (7) to determine whether a specific substance might be isolated from intestinal mucosa, which would inhibit gastric activity without having an effect on pancreatic and biliary flow. They were successful in preparing such an extract, although they found that similarly prepared extracts of muscle and gastric mucosa also caused inhibition, but to a less extent than extracts of intestinal mucosa. Because of the strong presumptive evidence, they considered the humoral inhibitory, or chalone, substance and the inhibitory substance in their extract to be identical. So, they named this gastric inhibitory principle of intestinal extracts "enterogastrone."

More recently, Lim, Ling and Liu (8) have reported that they have been able to remove all the vaso-depressor and toxic substances from the active extract. Independently, Greengard, Maison and Ivy (9) have also been able to prepare an extract which is free from objectively detectable toxic substances, and which inhibits both secretion and motility in the dog. However, it is believed that the preparation is not yet sufficiently pure to warrant injections into man.

It would appear that enterogastrone is a substance which may prove to be of practical value. Any substance which possesses the gastric inhibitory attributes of atropine without its undesirable side effects would be of practical value in certain cases of "peptic" ulcer. It is not known whether enterogastrone is active hypodermatically, which will depend largely on

its molecular size. If it is found that it must be administered intravenously, like secretin and cholecystokin, in order to obtain effective responses, its

practical therapeutic usefulness will, of course, be much more limited.

A. C. Ivy, Chicago, Ill.

## REFERENCES

1. Farrell and Ivy: *Am. J. Physiol.*, 76:227, 1926.
2. Lim, Loo and Lin: *Chinese J. Physiol.*, 1:51, 1927.
- Also Lim: *Quart. J. Exper. Physiol.*, 23:263, 1933.
3. Feng, Hon and Lim: *Chinese J. Physiol.*, 3:371, 1929.
4. Quigley, Zetzelman and Ivy: *Am. J. Physiol.*, 108:643, 1934.

5. Quigley and Phelps: *Am. J. Physiol.*, 109:133, 1934.
6. Kosaka and Lim: *Chinese J. Physiol.*, 4:213, 1930.
7. Kosaka, Lim, Ling and Lin: *Chinese J. Physiol.*, 6:107, 1932.
8. Lim, Ling and Liu: *Chinese J. Physiol.*, 8:219, 1934.
9. Greengard, Maisson and Ivy. Article in course of preparation.

## SECTION IX—Book Reviews

(This section is open to contributions from any medical reader, whether a member of the Editorial Council or not).

*This Journal is not responsible for the opinions, decisions or groupings expressed by reviewers of books or pamphlets. For the guidance of readers, an attempt is made to indicate the relative worth of reviewed material by placing "stars"—★ in connection with the reviews. The greater the number of "stars," the more agreeably and importantly has the book or pamphlet impressed the reviewer.*

★★★★ *Treatment by Diet*, by Clifford J. Barborka, M.D., Sc.D., F.A.C.P., Department of Medicine, Northwestern University School of Medicine, Chicago; formerly consulting Physician, Mayo Clinic, Rochester, Minnesota; 615 pages, Illustrated. Published, October, 1934, by J. B. Lippincott Company, Philadelphia, Pa. Price \$5.00.

Occasionally, without a lot of "just-wait-and-see-what's coming" type of publicity, a member of our profession quietly assembles his own and others' data in a particular field of medicine, discriminatingly evaluates the material in the light of an extensive clinical experience and private patient management, retains what is dependable, chucks out what is unproved or ephemeral, and then compiles a sincere, thoroughly useful, practical book.

Dr. Barborka has accomplished just that objective in his "Treatment by Diet": every page "makes sense" and this sense is carried to us in a scholarly, usable fashion.

McLester was the first of this country's internists to bring forward a book which considered diet not alone from its scientific and nutritional aspects but, what was more significant, diet such as Americans actually eat. He, it was, who brought us foods which are not foreign to our appetites and tastes and liberally supplemented with all sorts of patented, high-priced, unproved, faddistic, *ausländlicher* conglomerations whose attempted ingestion often proves enough to gag a buzzard.

Barborka has accepted McLester's rationality, and progressed from it not only to emphasize diet, *per se*, but to demonstrate dietetics as a medium of therapy on a par with treatment by drugs or other accepted modes of clinical and private patient management. He has performed this exceedingly difficult task in a useful, impersonal, unbiased, unprejudiced manner. Such method of considering food as a therapeutic agent, the reviewer feels is a distinct—and safely he may add, a definitely American—advance.

Perusal of many foreign (and some homeland) publications demonstrates that dietotherapy has seemed to be a field of activity in which the longer certain clinicians have dwelt, the greater have been their tendencies to develop fixed ideas, narrowed visions, faddism or the temptation to accept half truths and then to wander aimlessly over the horizon of fact into the nebulous realm of supposition, theory, fetishism. So general has been this tendency in books and in journals, that "dietetics"—whether in health or in disease—until the advent of McLester's, and now Barborka's, unique publications, has meant little more than "just another diet-book," bywords among doctors. Their bookshelves carry a dozen or more volumes on the topic, many of the works "practically new," rarely used, pages uncreased, often even uncut. All of which eloquently indicates that, with rare exceptions, diet as a form of therapy either has been presented miserably to the practitioner who, as his shelves show, is eager to learn how to employ it in every-day practice or that dietotherapy admits of maintaining so few positive positions that responsible writers have shunned the subject. Those who have risked stretching their theses to book length, largely have been copyists, meagre in experience, purveyors of spurious or half baked facts, or have written merely for posterity: for certainly, little of what they have set down is read by, or has been found acceptable to, the present generation of physicians still able to cerebrate or possessed with a sense of values—or of humor!

Dr. Barborka's method of approach is distinctive and logical. First, a concise discussion of diet as it is essential to the maintenance of health is given. Here the economy of words is commendable, but even so the subject in all its phases adequately is covered. "Parts I and II" limited to 42 pages embrace as much fundamental material as usually one finds elaborated to make a fat tome. Somewhere in the Author's ancestry must lurk a bit of Scotch, for few words are wasted. Rarely has the reviewer observed such a lot of matter comprised into so few pages. The discussion admirably qualifies the reader to progress to "Part



III"—the chief reason for publishing the book—namely, "Diet in Disease."

In this section of approximately 500 pages, we are given a most helpful—and to us—an original manner of presentation of the treatment of disease by diet. Each disease or syndrome is headed by a "box" which contains a pertinent summary of the pathologic aspects (when possible) or the *nature of the disease* and the *object of diet* in its treatment. These summaries are appreciated at a glance while, below, the text gives briefly the essential clinical features of the ailment and sets forth the important factors bearing upon the significance of diet as an agent concerned with treatment. Prior to presenting specific diets, the effects or the correlation of medicinal or other modes of management which many be exhibited, judiciously are discussed. The variation in clinical signs and symptoms and the bearing of such upon dietetic changes are emphasized. Incidentally it may be observed that in these considerations, the Author exhibits a sound knowledge of the basic clinical manifestation of disease.

The diets, themselves, are extremely well presented, not alone from the standpoints of their caloric values, the relative quantities of protein, carbohydrate and fat, but they comprise refreshing varieties of food stuffs; the addition of tabulations indicating simple, easily followed, household measures, makes particularly helpful the quantitative allowances of food stuffs to physicians, nurses or other attendants who are not trained to the accuracy called for by scale-weighing or have not suitable scales available. Photographs illustrative of kinds, varieties and quantities of foods furnish visible and not easily forgotten impressions of what constitute suitable, correct and therapeutically adequate meals.

Especially complete and sound are the discussions of the treatment by diet of disorders of metabolism—diabetes mellitus, gout, obesity, and emaciation. In this grouping, the Author chooses also to include nephritis, an ailment which other clinicians may include in other classifications, but, in view of recent knowledge supplemented by Dr. Barborka's discussion, justification for so doing reasonably is admissible. At any rate, his presentation is excellent and more than usually definite.

The Sections devoted to the anemias, peptic ulcer, constipation and "deficiency diseases" (an ever expanding list—a list whose individual components in not all instances is yet so sharply defined as one would like and in which future years may qualify its length by enlargement or limitation) represent not only the down-to-date conceptions of conservative experienced clinicians, but include not a little original thought on the part of the Author. Personally, the reviewer would wish for a rather more liberal discussion of the dietotherapy in peptic ulcer than one obtains, but on the whole, Dr. Barborka satisfactorily presents popular conceptions and simply followed instructions with regard to feeding.

Probably the Author nodded a bit (who would not when "boiling down" for practical use the immense literature and material on this and other topics comprising this book?) when he states as one of the dietetic precepts in ulcer management, "avoid foods that stimulate gastric secretion" and then follows by including "protein foods" as "desirable" inasmuch as "they (milk and eggs) bind the free hydrochloric acid

present in the stomach and aid in neutralizing the acidity." Recent researches, particularly those of Babkin and his Associates at McGill University as well as those of observant clinicians for more than fifteen years past (Jarotsky and others) have demonstrated that the proteins of milk and of egg stimulate both acid and pepsin secretion in excess of their capacity to combine with the digestants so stimulated. The fluid protein of milk is less stimulative than is the semi-fluid protein of egg: in fact, if one employs egg in ulcer diet, the investigations of Rehfuess and Hawk would indicate that chopped, hard-boiled egg most satisfactorily "binds" free acid and most readily "neutralizes" peptic activity. Very likely, the "milk and soft egg diet" used in the dietotherapy of gastric ulcer owes whatever efficacy it may have by being fluid and thus, rapidly passing from the stomach and the duodenum so that in the lower duodenum and upper jejunum digestion may take place, thereby leaving the stomach (and the duodenum—the most common site of ulcer) relatively at rest. Digestion of a milk and egg mixture in such position in the alimentary tract may permit production of the hormone-like, gastric secretion, inhibitory agent "Enterogastrone" isolated by Ivy. Hence the "milk and egg diet" for gastric ulcer treatment proves to be put indirectly advantageous. All in all, the consensus of clinical opinion regarding the initial diet for gastric ulcer management, when there exists no pyloric obstruction, continued spasm or organic blockage, rationally would seem to consist of fluid or semi-fluid carbohydrates and fats (Babkin, *et al* and, most recently Armine Alley).

However, Dr. Barborka—as stated—has clung to popular concepts in ulcer dietotherapy and, as happens so commonly, with the majority of clinicians, has designated no particular variation in diet for duodenal ulcer—the most common "peptic" lesion. It is significant of the times, that the Author has stressed the need for vitamins in ulcer diet and has cautioned against the needless, and often reckless, exhibition of alkalies. Therapy by "gastric mucin" (really a food and not so "protectant" a medicinal agent as was first extolled by its proponents) properly receives non-committal comment. Its more easily ingested vegetable prototype "Oktrin" is not mentioned. Dr. Barborka's "Ulcer Diet" lists are quite adequate; especially helpful should prove those submitted for dietetic management following operative interference.

Very rational for the aid possible *via* diet are the suggestions given for care in circulatory and febrile ailments, tuberculosis, disturbances (non-ulcerative or malignant) of the oesophagus, stomach, biliary tract and liver and the intestines.

Especially valuable is the consideration of the Ketogenic Diet and the disturbances in which it is applicable. Here the Author speaks with especial authority, for probably no other clinician has been so great a factor in its origination, modification and exhibition as he. Perhaps, for the first time, he has presented our profession with reliable examples of this type of diet in the therapy of epilepsy, migraine, asthma and chronic urinary infections. And with it all—despite his close connection with the elaboration of the Ketogenic Diet—Dr. Barborka has been rational and conservative to a degree refreshingly acceptable. In fact, this Section demonstrates, more than any other in the



book, how firmly balanced is the Author's conceptions of dietotherapy. More than ordinary equilibrium is demanded when one considers a subject very close to his heart or in a field where one has so notably pioneered as has Dr. Barborka in the practical application of the Ketogenic Diet for relief of a troublesome group of pathologic syndromata.

But ten pages are devoted to "Food Allergy"—a significant fact in view of the Author's broad grasp of principles of dietotherapy. Such limited allotment of space should serve notice as to the extent of our actual knowledge of what really is known and is clinically available in the dietetic therapy of that bewildering group of disturbances which certain individuals have designated, "allergic." The essentials, however, are contained in Dr. Barborka's ten pages. Whole volumes and an enormous journal literature have been written on unproved and multitudinous and confusing aspects of what within a decade has created the so-called specialty of "Allergist."

Skin lesions, arthritis, pregnancy and lactation, dental caries and routine hospital diets (a subject well handled, but which always causes "goose-fleshing" to the reviewer inasmuch as he personally shudders at the idea of adapting an ill patient to any routine "diet") doubtless, a necessity in a book which aims to cover the subject and satisfy everyone, and special methods of feeding conclude this encyclopedic modern discussion of treatment by diet.

There is a very complete index; the bibliography is extensive and well selected; the index proved accurate to twenty tests.

The book is a characteristic Lippincott product: convenient in size, of appropriate weight, well bound, made of satisfyingly white paper which well takes type impressions, typographically attractive, well "proof-read" and reasonable in price (a very welcome feature in these days so financially discouraging to physicians).

The reviewer cannot recall when so much usable, accurate, dependable, down-to-date knowledge—particularly on dietotherapy—has been offered to doctors, nurses, hospitals, investigators, medical students, internes, so well arranged, so authoritative and for so little cash.

Furthermore, he is unable to see how anyone who desires seriously to employ diet in the everyday treatment of disease, can feel comfortable in his practice without Dr. Barborka's really admirable book. Both to Author and Publisher is our profession indebted, for they have given us a really standard, authoritative work—one which we venture to prophesy will command wide acceptance and will enjoy many future revisions to meet changing conditions in a very labile but necessary field of practice.

Frank Smithies.

★ ★ ★ *Cirugia Gastrica*, Volume 1, by Dr. M. Corachan, Barcelona, Salvat Editions, 1934.

Here is one of the most remarkable books we have seen in a long time. It is not only well written and beautifully illustrated with many photographs in color, but it is bound and gotten up like a presentation copy.

The author is professor of surgical pathology at the University, and chief surgeon to a large hospital

in Barcelona. It is remarkable for a European book that the large bibliography contains abundant references to the work of men, not only in Spain, but also in France, England, Germany and the United States.

It is unfortunate that few American physicians can read Spanish, because otherwise this book would make a nice addition to their libraries. As far as we know there is no book in English which covers the field so extensively or so beautifully as this volume and its companion, which will appear later, will do.

Much space is given, as one would expect, to the problems of ulcer and cancer of the stomach. Much space is given also to a discussion of the rarer lesions of the stomach.

The only criticism that we feel inclined to make is that we wish the writer had trusted more to his own experience and wisdom and less to his extensive knowledge of what others have written.

The second volume is to contain a chapter on pre and post-operative care, on anesthesia, indications for, and technique of, the various operations on the stomach rare or disused operations on the stomach that have been operated on and the results of various operations, and on the bad results sometimes obtained after gastro-enterostomy and gastrectomy.

Walter C. Alvarez, Rochester, Minn.

★ ★ ★ *Food for the Diabetic*, by Mary P. Huddleson, Consulting Dietitian. The MacMillan Company.

This book was written for the diabetic patient. In 103 pages it well fulfills its purpose in giving the patient all the information needed to carry out the instructions and the program outlined by his physician. Throughout the book the patient is impressed with the importance of frequent visits to his physician. Probably one of the most important points of emphasis is the diabetic program which is so definitely outlined in the first part. In this program, detailed instruction is given the diabetic patient for his daily care, how to prevent emergencies, and how to meet emergencies should they occur.

The book is divided into three sections: Section 1—Diabetes; Section 2—The Diabetic Diet; Section 3—Details for the Diabetic Diet.

In Section 1, emphasis is placed upon the diabetic diet meeting the requirements of the normal diet. The Author gives full explanation as to what a normal diet must contain. A simple definition of diabetes is given and the subject is discussed very clearly from the standpoint of the layman.

In Section 2, detailed instruction is given in measuring foods, how to calculate the food prescription, food-tables, meals for the diabetic and recipes for the diabetic are also clearly outlined. A method is given for working out the diet according to the physician's food prescription for the total carbohydrate, protein and fat. In the tables of food equivalents the amounts are expressed in gram weight and in common household measurements—standard half pint measuring cup, tablespoon and teaspoon. The size of a slice of bread or meat and the diameter of certain fruits are given in inches. Very practical recipes are given which the patient is taught to calculate in his daily diet prescription.

\*Editor Journal American Dietetic Association.

In Section 3, a good description is presented on how to test urine and how to give insulin. In the last chapter good suggestions are given on the prevention of diabetes, especially in those families or races where there is a tendency to diabetes.

This book offers a very clear understanding of the diabetic diet, and many variations which may be made from a diet prescription. The plan of the instruction outlined is very clear to the patient who has been taught by this method. The writer has stated that there are several methods for the calculation of dia-

betic diets "each easy for the originator but difficult for others." Therefore should a patient, who has been taught by some other method than the Author outlines be given this book for further instruction in planning his diet, he would probably be much confused.

Other subjects treated in the book should be most valuable to any patient with diabetes regardless of the method he has been taught to calculate his diet and plan their daily menus.

Clifford J. Barborka, Chicago, Ill.

## SECTION XII—"The Clinic"

### Dyspepsia and Gastric Bleeding Due to Chronic Appendicitis

By

MARKS S. SHAINÉ, M.D.

219 W. 70TH ST., NEW YORK CITY, NEW YORK

FOLLOWING the huge number of appendectomies which were performed indiscriminately on the most meagre evidence in the early years of this century, there set in a violent reaction in which the whole concept of chronic appendicitis as a clinical entity and as a cause of dyspepsia was entirely rejected. The profession is but now awakening to the fact that the pendulum had on both occasions swung too far, first one way then the other; the truth regarding chronic appendicitis is emerging more and more clearly. Many skeptics still deride the diagnosis of chronic appendicitis whether made on the basis of clinical signs and symptoms or of a roentgenological study.

The unbiased observer who has followed the literature on the subject and who has had the opportunity to observe the abrupt and permanent disappearance of a chronic "dyspepsia" following appendectomy will no longer deny the casual relationship between the two conditions. But it is far less widely known that a chronically diseased appendix may be the cause of gastric or intestinal bleeding in the absence of other gastro-intestinal disease. Attention to this fact has been drawn by several writers (1, 2).

The following case history offers evidence, proved at operation, that a chronically diseased appendix may

cause not only intermittent attacks of dyspepsia but also gastric bleeding.

#### CASE REPORT

S. G., aged 58, referred by Dr. Jacob Sobel, gave a history of anorexia dating back to 1922. He first presented himself for examination on July 6th, 1926, complaining that for four weeks he had had pain and burning in the epigastrium and left hypochondrium, which began two hours after meals and were relieved by soda. He also complained of belching, sour regurgitations, constipation and loss of weight.

Physical examination showed a pale, thin man, five feet eight inches in height, whose weight was 109 lbs., neurologically negative, a blood pressure of 130/80, heart and lungs nega-

tive, abdomen negative, no tenderness in *McBurney's* region. Except for some internal hemorrhoids, the sigmoidoscope was negative.

A gastro-intestinal X-ray examination was negative except for ptosis and a small gastric residue at six hours. He was put on a high caloric diet with sufficient roughage, oil enemata, mineral oil and tonics. His symptoms improved and he was discharged in December, 1928. His weight was 120½ lbs.

He was next seen in April, 1929, with symptoms very similar to those complained of in 1926. X-ray examination showed a definite and constant deformity of the duodenal cap, and a six hour gastric residue. He was put on ambulatory ulcer treatment and was discharged, improved, after four weeks.

In November, 1930, his symptoms returned and the X-ray examination again revealed a constant duodenal cap deformity.

After a month's treatment similar to that in the preceding attack, his symptoms were relieved and he did not return until November 9th, 1933. He now complained of heartburn, sour regurgitation and vomiting of coffee colored material which gave a positive benzdine test. The Ewald test showed a hyperacidity and a positive benzdine test. Lavage showed a large gastric food residue six and seven hours after a meal. His weight was now 109 lbs. The X-ray examination showed a narrowing and a deformity in the pyloric region. The duodenal cap was poorly filled and there was puddling in the second portion of the duodenum. It was decided that the patient had either a large ulcer or a new growth.

With the hope that it was an ulcer, he was put to bed for three weeks on a Sippy regime and his symptoms subsided. But ten days after he left the hospital, the distress, the heartburn and the coffee colored vomiting returned. He was re-admitted to the hospital.

A laparotomy was performed by Dr. Louis Friedman. The stomach and duodenum were found absolutely normal. There were no thickening, no induration, no deformity and no sign of adhesions. The gall bladder, liver, pancreas and colon were normal, with no adhesions. The distal half of the appendix was distended to about three times its normal width and it contained a large fecolith. Appendectomy was performed. The patient made an uneventful recovery. He has remained well since the operation, has no symptoms and has gained over ten pounds in weight.

#### SUMMARY

The history is presented of a patient who for years had digestive

symptoms with hematemesis. The X-ray showed a deformity in the stomach and duodenum. Laparotomy showed no pathological lesion except a diseased appendix with a large fecolith.

#### REFERENCES

1. E. L. Bortz: Diffuse Hemorrhage from the Stomach. *Arch. Int. Med.*, 50:1 (July) 1932.
2. Thomas R. Brown: The Results of Treatment in Gall Bladder Disease. *Am. J. Dig. Dis. and Nutr.*, 1:4 (June) 1934.

## CHRONIC AMEBIASIS, EXHIBITING DYSENTERY FOR THIRTY YEARS

By

M. A. DESMOND, M.D.  
SANTA MONICA, CALIF.

CASE report: Patient, L. H., male, Spanish War Veteran, age 66, white.

Submitted Nov. 8, 1934.

# The new LAROSTIDIN TREATMENT

for peptic ulcer . .

The Larostidin Treatment consists of consecutive daily intramuscular injections of 5 cc. (1 ampul) each, for an average length of time of about 24 days. Inject alternately in arms or gluteal muscles, preferably the latter. The injection should be made slowly, with gradual withdrawal of the needle . . . . .

*Hospitalization is not necessary  
No interference with normal everyday routine*

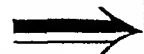
*Indeed, many cases hospitalized prior to the beginning of treatment become ambulant before the injections are all given—and there is no rigid dietary schedule or interference with the patient's normal everyday routine.*

#### TYPICAL MANIFESTATIONS

- (a) After about 4 or 5 injections—pain usually disappears.
- (b) After about 10 days—average diet is tolerated.
- (c) At end of treatment—there is usually remission of all symptoms: food intolerance, gastric pain, hyperacidity; improvement indicated by normal peristalsis and emptying time; absence of spasticity.



Make  
this test



Take five of your peptic ulcer patients of longest standing, patients who have resisted other treatments or have had recurrences. Explain the Larostidin treatment, and the success being reported with it. Note the daily reports of those who take it; and at the end figure your percentage of successful treatments for the group. We are confident you will use Larostidin thereafter.

AMPULS, 5 cc., cartons of 6.

**HOFFMANN-LA ROCHE . . Nutley, New Jersey**

March 20th, 1934, this patient was bedridden, extremely attenuated; very weak; abdomen distended; no indication of color to the skin; bowel movements from 10 to 25 per day; weight 100 pounds; mentally depressed; hemoglobin 27%; color index 0.9; leucocytes 5,600; erythrocytes 1,140,000. The blood smears showed of 100 cells counted, lymphocytes 28, large mon. 6, poly. 65, basophiles 1. The Wassermann was negative. The stool revealed cysts of ameba hist. My diagnosis was chronic amebiasis, chronic colitis, severe secondary anemia. At this point I may say that Mr. H. was former hospital steward in the Philippines and Mrs. H. a nurse. The dysentery began in 1904 at Manila, P. I. (See last paragraph).

The following medication was ordered; 20 min. liquid Alpha Naphco hourly in water and orange juice supplemented by 12 Enteric Coated Capsules of the Jelly of Alpha Naphco, daily.

The third night after beginning medication, the dysentery was checked to the extent that Mr. H. had no b.m. during the night, and thereafter the number of b.m.'s. was greatly reduced. He continued on the above mentioned treatment until the 11th of April, at which time his condition was much improved, hemoglobin 40%, b.m. 1 to 2 daily, patient sleeping well, appetite returning, color returning, psychically much encouraged, in fact patient was now up and about the house. Lextron was now ordered. May 15th hemoglobin 60%, weight now 155 pounds and color good. May 28th hemoglobin 68%, weight 156½ pounds. After the 5th of June, the patient discontinued the ingestion of the germicidal medications i.e. Alpha Naphco liquid and the capsules, but continued on Lextron.

His present weight is 174½ pounds, eats and sleeps well, b.m.'s 2 to 3 daily. The laboratory report on two recent stool examinations ran as follows: feces semi-solid formed, light brown color, normal appearance; benzedine reaction for blood, negative. Microscopic examination revealed neither active nor encysted forms of any type of protozoa.

In connection with the above case, I wish to quote the data of an examination of date, May 25th, 1931, as given me by the Case Correspondent, War Service of the American Red Cross as follows:

## CELLU CANNED FRUIT JUICE-PAK



A new product consisting of choice tree ripened fruit packed, without the addition of sugar, in fresh undiluted juice expressed from fruits of the same kind.

### DIETARY USES

Diets in which a sugared product is not desired, quantitative diets in which a fruit of known food value is recommended, diets which stress mineral value are particularly mentioned as mediums to which Juice-Pak Fruits are particularly adapted. The use of Juice-Pak Fruits in quantitative diets for Diabetics helps to maintain a less variable source of Carbohydrate value than is possible in using fresh fruits. The total available Carbohydrate values are listed here for your information. The Carbohydrate, Protein, Fat and Mineral values are stated on the labels of all Juice-Pak Fruits to facilitate their accurate computation in the diet.

### Carbohydrate Values

|                     |     |
|---------------------|-----|
| Apricots            | 11% |
| Blueberries         | 10% |
| Royal Anne Cherries | 14% |
| Yellow Cl'g Peaches | 9%  |
| Bartlett Pears      | 11% |
| Sliced Pineapple    | 15% |
| Crushed Pineapple   | 13% |
| Pineapple Juice     | 13% |
| Red Raspberries     | 9%  |
| Strawberries        | 7%  |

We would like to send you more information on these Fruits.

Pin to your letterhead and mail.

Send us a catalogue describing Juice-Pak Fruits.

D. D. N. 3-35.

**Chicago Dietetic Supply House, Inc.**  
1750 W. Van Buren Street Chicago, Illinois

"2nd par. The last examination dated May 25th, '31, shows myocarditis with hypertension, chronic cholecystitis, chronic pleuritis, severe anemia, generalized arteriosclerosis, defective vision, hallux valgus, chronic nephritis, suspected thyroid trouble."

"3rd par. He was treated for dengue and amoebic dysentery at the Civil Hospital in the Philippines, 1904."

The above case is reported because of its unusual interest, indicating, as it does some of the results of prolonged amebic depentery.



## A Relapse in Pernicious Anemia is Dangerous

## CHAPPEL'S LIVER EXTRACTS

both Oral and Subcutaneous, are of reliable, uniform potency. Each batch of the latter is tested clinically before being released for sale—an added assurance of its dependability. (Both products are Accepted by the Council of the American Medical Association).

**LABORATORIES CHAPPEL BROS, INC.**  
ROCKFORD, ILLINOIS

# SECTION I—*Clinical Medicine: Diseases of Digestion*

## Vaccine Therapy in Ulcerative Colitis\*

*Thesis By*

SIBRAND LUPS (Arts)†

GRONINGEN, HOLLAND

*Translated and Edited by*

ABEL J. BAKER, M.D., F.A.C.P.

GRAND RAPIDS, MICHIGAN

### HISTORICAL REVIEW

CLINICAL cases of ulcerative colitis which differed considerably from the types of dysentery usually encountered, in the fact that they did not respond to medical treatment, were first reported in the latter part of the previous century. Until about 1902, it was mainly surgeons who observed and described the characteristics of this condition. The great similarity of this disease with dysentery, however, often led to much confusion. It is, therefore, not to be wondered at that many clinicians considered the affection as a peculiar form of dysentery. Even until recently, opinions on the question as to whether or not ulcerative colitis is an independent disease have been much debated. Its chronologic development, therefore, can hardly be discussed, hence, a review of the various opinions by different clinicians is not based on any chronological order. Those investigators who have expressed opinions as to whether or not ulcerative colitis strictly is a disease entity can be divided into three groups as follows: (1) Those who considered it as belonging to the group of dysenteries. (2) Those who, in some respects, considered it an independent disease but nevertheless admitted many arguments against this view and therefore still considered it as one belonging to the group of dysenteries. (3) Those who considered it strictly as an independent disease.

In the latter part of the nineteenth century most clinicians considered this affection which later was called "ulcerative colitis" as belonging to the dysentery group, even after 1903, when Boas expressed the view that ulcerative colitis was an independent disease. About 1914, however, there was a marked change in the viewpoints of many observers on this question although many still felt that it was of dysenteric origin. They knew full well that only in a few cases true dysenteric organisms were found. Moreover, the therapeutic effect of anti-dysenteric serum inclined them to the view that it must be of such origin. This view, furthermore, was supported by the fact that,

during the late war, only in 1/3 of the cases in which the diagnosis of dysentery was clinically confirmed were the known dysenteric organisms recovered. Among the observers supporting this opinion were Strausz, Leusden, Hurst and Schur.

Another group of investigators took a rather questioning attitude on the subject. On the one hand the fact that the dysentery bacillus was so infrequently found in ulcerative colitis and also the fact that the illness ran a course peculiarly its own inclined them to the belief that it had an etiology of its own. However, they did not consider this a sufficient criterion to support such a view. Moreover, these men considered it not unlikely that the cause of ulcerative colitis might be an unknown variant of the dysentery group of organisms. Strausberger and Udaondo were inclined to view the condition from that standpoint.

Rollaston took a different stand. He considered ulcerative colitis to be a non-specific disease and argued that various microorganisms might play a rôle in its production. He called it a *syndrome* in which the clinical findings were quite constant but in which the anatomical changes were markedly different. Boas, who named the disease "ulcerative colitis", was the first investigator to consider it as a clinical entity. In an article appearing in 1903, he called attention to the many points of difference existing between this condition and true dysentery.

At first there were few who agreed with Boas in this view but gradually others joined him in the belief that he was justified in separating ulcerative colitis from the dysentery group. One of his strongest supporters, Ad Schmidt, wrote an article in 1914 summarizing all the important reasons for considering ulcerative colitis a separate entity. Because of its cryptogenetic character, he advocated separating colitis from all those intestinal infections in which pathogenic organisms were known to be causative.

Zweig and Albu, among others, were of the opinion that ulcerative colitis was a separate and independent disease brought about by specific microorganisms. Many investigators who held this same view have searched for the true etiology but this work has always been very difficult because of the numerous bacteria present in the intestinal tract, saprophytes as well as pathogenic organisms. Further, the fact that

\*Submitted to the faculties of the National University at Groningen, in candidacy for the Degree of Doctor of Medicine, on the authority of the Rector Magnificus Dr. H. W. C. Bordewyk, Professor in the faculty of Jurisprudence. To be defended before the faculty of medicine on Wednesday, July 11th, 1934, at 4:00 o'clock in the afternoon.

†Courtesy of the Author and J. B. Wolter, Publishers Groningen, The Hague, Batavia, 1934.

Submitted for publication August 10, 1934.

in the study of a certain pathologic process, unless some specific organisms are present in large numbers, one cannot draw definite conclusions concerning the causation. It is also well known that many organisms, normally saprophytes, may assume pathogenic properties and thus cause disease. Bassler and Rosenheim have ascribed to the colon bacillus etiologic importance in this condition. They believe that the colon bacillus can become very virulent and, in their opinion, ulceration might result through the activities of the colon bacillus in association with a streptococcus.

Lockhart-Mummery is of the opinion that not only the colon bacillus and the streptococcus but also the diplococcus of pneumonia might be a causal agent. He reasons that the pneumococcus might be instrumental in causing the hemorrhagic type of ulcerative colitis. This pneumococcus infection he considered primary and not a complication of pneumonia. Many other organisms have been considered in a study of the etiology of colitis such as the streptococcus, gas bacillus, the *bacillus enteritidis* of Gärtner, the *bacillus proteus vulgaris* and the *bacillus pyocyaneus*.

Bargen held that the gram-positive, *diplo-streptococcus* which he isolated from the ulcers of patients with this disease was the etiologic factor. As we shall try to make clear in the following, we believe that on the basis of bacteriologic, clinical and experimental evidence, there is good ground for supporting Bargen's contention.

We have already mentioned the fact that, in 1903, Boas called this clinical entity "ulcerative colitis". Other observers, however, have objected to this term and have substituted others which they considered more typical of the condition. Ad Schmidt, because of the very frequent presence of pus in the majority of the cases, called it "colitis suppurativa." Friedel attempted to introduce the term "colitis hemorrhagica." Rosenheim chose the name "colitis ulcerosa gravis."

Not always, however, is there pus formation in colitis and in even serious cases it may be present in only very small amounts. Neither is the presence of hemorrhage a constant symptom. The name "colitis gravis" may often be correct but, on the other hand, many cases of colitis run a fairly benign course. Differences of opinion on the characteristics of the disease are thus shown in the variety of names which have been given to it. I rather feel that the original name "colitis ulcerosa" is fitting if one does not lose sight of the fact that ulcers appear only at certain stages of the pathologic process, while the additional word "chronic" must be considered in connection with the tendency of the disease often to show chronicity.

#### THE PURPOSE OF THE INVESTIGATION

As we have already mentioned, Bargen, of the Mayo Clinic, reported considerable work on the isolation of gram positive diplococci from ulcers of patients suffering with ulcerative colitis. On the basis of animal experimentation, he considered these organisms the cause of this disease and on this basis made autogenous vaccines with which he obtained excellent results in the treatment of his patients. This successful work led us to introduce vaccine therapy in the treatment of patients we saw at the Groningen Clinic.

#### CLINICAL SIGNS AND SYMPTOMS OF ULCERATIVE COLITIS

The picture of ulcerative colitis consists of a number of clinical symptoms of greater or lesser gravity,

depending on the seriousness of the intestinal disturbance and the stage of the disease. Efforts have been made to distinguish different clinical forms of the disease-process in harmony with certain symptoms, but this is not practical as the various manifestations are only evidences of *different stages* of the disease. It now is considered much more rational to think of these different stages as the result of *one disease process*. Only the most important symptoms will be considered in this paper.

#### SUBJECTIVE COMPLAINTS

Generally the patient complains of *pain* which may be felt over the entire abdomen, or only over certain areas. Frequently, the pain is located in the region of the sigmoid but it is not rare to have it quite definitely outlined over the entire colon. The pain, which varies a great deal in intensity, frequently becomes more intense and colicky before defecation. After the bowels move there is generally considerable relief. Udaondo attributes the colic to colon spasm. Frequently, in cases associated with meteorism, there is much colic and abdominal noise; here passage of flatus brings relief. In some patients there is marked tenesmus, which however, does not differ from that which is found with many other intestinal conditions. *Distention* often is a troublesome feature and is aggravated by movement. Rest in the dorsal position generally gives relief.

#### GENERAL CONDITIONS

The intestinal disturbances brought on by ulcerative colitis apparently do not always affect other bodily functions, so we may observe very few general symptoms. Generally, however, we do have some, depending upon the onset and violence of the infection. In the acute or sub-acute case there is more or less *rise in temperature* which may be intermittent or continuous, or according to Schmidt, may show a septic curve indicating a general infection. In those cases running a chronic course, the temperature is generally normal but associated, occasionally, with slight elevations indicating a lighting up of the disease process.

Even advanced departures from the normal colon, in long standing cases, are often accompanied with good general nutrition. Only slight pallor and the passage of mucus betray impaired health. However the majority of chronic cases show *weight loss*. The patient is exhausted and has an anxious expression. Changes in the intestinal excretions almost immediately are reflected in his general condition. When the diarrhea improves, either spontaneously or following treatment, the patient responds very quickly; he improves and takes on weight.

#### DISTURBANCES OF DEFECATION AND ABNORMALITIES OF THE FECES

The most common complaint is *diarrhea*. In considering this symptom one must differentiate between an "essential" and an "apparent" diarrhea. The latter, it must be remembered, continually exhibits evidence of some pathological products in the discharges. The passage of frequent stools in some cases is the only subjective symptom. The diarrhea may be of sudden onset leading one to a diagnosis of "acute catarrhal gastro-enteritis". Later, other evidences of ulcerative colitis appear. Sometimes periods of apparent well-being alternate with periods of diarrhea. The picture may be a very innocent one until the



Fig. 1. Normal mucosal foldings.

Fig. 2 A. Section of transverse colon with coarse transverse folds; longitudinal folds entirely absent. Descending colon and sigmoid colon show honey-comb structure.

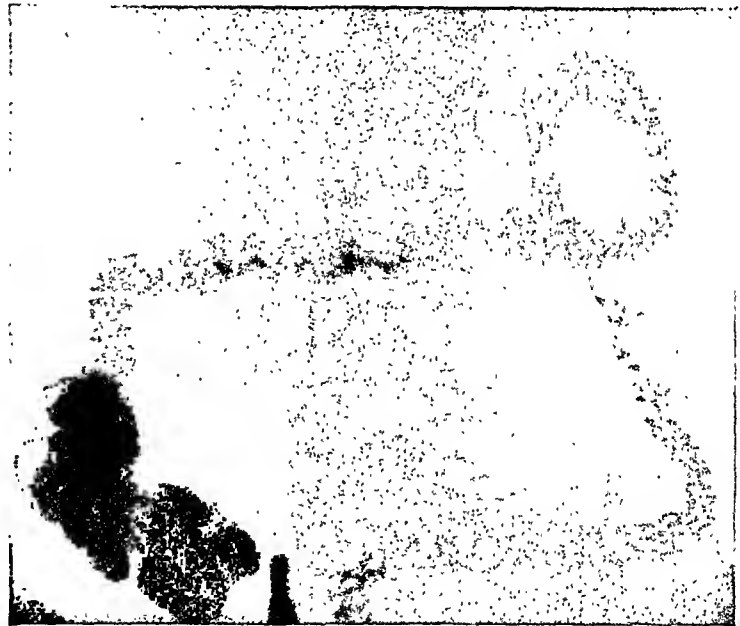


Fig. 2 A.



Fig. 2 B.

Fig. 2 B. Coarse transverse folds; longitudinal folds missing.



appearance of sanguino-purulent feces betrays its seriousness. Albu reports the onset to be such in the majority of his cases. The stools may number nine to ten daily but may go to fifteen or twenty. The location of the lesions has considerable influence on the number of evacuations. In involvement of the lower end of the colon, tenderness and frequent urge to defecate are common, although very little fecal matter is expelled. Udaonda declares it not unusual in such cases to find a persistent obstipation even though there is a frequent desire to defecate. This so-called diarrhea is then a misnomer.

### THE FECES

In most cases the expelled material consists only of pathological substances, such as blood, mucus, and pus, containing very small amounts of fecal matter. In those cases in which the lesions are localized in the upper part of the colon, the stools are thin and of soup-like consistency. Pus, mucus and blood in their passage down becomes more intimately mixed with the intestinal contents and may undergo various changes. Only when they pass through the bowel rapidly are they found as such in the feces. On the other hand, in a recto-sigmoiditis, these abnormal constituents are not mixed with feces at all. The presence of pus in the stool, according to Udaonda and Schmidt, is the most characteristic and constant finding. According to these observers, it is always found if persistently looked for. Pus in very small amounts may be intimately mixed with feces and its detection even with the microscope is, in such cases, not easy, however, its finding is of such fundamental importance that it is very necessary in all stages of the illness even during convalescence. Also, where blood is present in quantity as in the "hemorrhagic form" of colitis, the presence of pus may easily escape detection. Albu maintains that the presence of pus in the stools is not a constant symptom in ulcerative colitis. In many of his patients he could not demonstrate it. This agrees with our experience as we often search for pus in vain. But in patients with demonstrable ulceration, pus is always present. Microscopic confirmation of this finding is absolutely necessary inasmuch as mucus may resemble pus, macroscopically. It is particularly in the acute catarrhal stage of ulcerative colitis that stools may consist largely of blood, and blood loss may be large. When improvement follows, macroscopic blood disappears rapidly, although the frequency and contents of the evacuations may still be quite abnormal. For long periods, blood can be shown spectroscopically. It is sometimes quite remarkable how well patients may appear even after losing large quantities of blood. Mucus is present in both mild and severe cases. In the acute stage, it often is entirely absent.

The stool generally is weakly alkaline in a well established case. Auba, Schmidt, and Lohrsch frequently found eosinophile cells and also Charcot-Leyden crystals.

### PHYSICAL EXAMINATION

The abdomen of a patient with ulcerative colitis may be of normal contour but may be, as a result of meteorism, quite distended. Usually, however, it is flat or even retracted. If the abdominal wall is soft and allows deep palpation, one often may palpate certain parts of the colon, contracted and slipping away from the examining fingers. The descending colon and

the sigmoid, are very often palpable, inasmuch as the disease process is there generally localized. In severe cases, abdominal distention prevents deep palpation. If one is fortunate and able to overcome this difficulty, one finds the entire colon extremely sensitive to pressure. The distention and the pain which palpation elicits, are probably the result of a pericolicitis of an inflammatory character. In those cases which exhibit a febrile course, with toxic manifestations, very often a slight swelling of the spleen can be demonstrated.

### EXAMINATION OF THE RECTUM

Digital examination of the rectum is of the utmost importance, because it may reveal conditions such as polyps or carcinoma, which often present symptoms strikingly similar to those of ulcerative colitis. Rankin, Bagen and Buie, give a careful account of their experiences in this connection. Generally, the rectal sphincter is spastically contracted and introduction of the examining finger is often difficult and painful. The most satisfactory position is the knee-elbow. The buttocks are separated and the vaseline-coated finger introduced at full length with the palmar aspect toward the bladder after which the finger is carefully rotated about 180° and pushed in the direction of the *plica rectosigmoidea*.

In the early cases of ulcerative colitis, the mucosa feels slightly roughened and one gets the impression of palpating a velvety surface. In later stages of the disease, one meets with irregularities, such as slight elevations on an otherwise smooth surface. If narrowing has taken place in the rectum, this is easily felt and one can generally outline the nature and extent of the stricture; withdrawal of the palpating finger often reveals blood, mucus and pus.

### BLOOD PICTURE

The blood examination seldom gives any characteristic findings. A lowered hemoglobin content is often shown. The anemia, however, is generally mild. A hemoglobin estimation of 28%, as reported by Udaonda, is an exception. In cases with much blood loss, the erythrocytes may show marked falling off. A slight leucocytosis ranging from eight to fifteen thousand is often present. Differential count is not particularly abnormal. Anemia sometimes met with in severe, long-standing chronic cases of ulcerative colitis, often is accompanied with marked cachexia. However, as autopsy has taught us, a wrong interpretation of this sign may lead to a diagnosis of carcinoma.

### PROCTOSCOPIC EXAMINATION

This method of examination also is necessary for the differential diagnosis of those conditions which are detected only by visual examination. If circumstances permit, it is desirable to make proctoscopic examinations at frequent intervals during the entire course of the illness. In this manner, one is enabled to visualize the various changes in the mucosa, particularly in the rectum and sigmoid and also to determine whether a temporary improvement in the general condition of the patient is associated with actual healing of the lesions. If, in spite of clinical improvement, the local lesions remain unchanged, we know it is only apparent and not real. In the presence of a recto-sigmoiditis, such examinations are always painful and a local anesthetic is necessary. Ordinarily a two to ten per cent solution of cocain or novocain is used.



Fig. 3.



Fig. 4.

#### BARUIN ENEMA ROENTGENOGRAMS:

---

Fig. 3. Catarrhal stage; honeycomb structure.

Fig. 4. Ulcerative stage; descending colon narrow and stiff. Haustrations missing; borders show saw-toothed appearance.

Fig. 5. Descending and sigmoid colon appear like a stiff tube. At operation, intestinal wall was markedly infiltrated and mucosa practically absent.

---



Fig. 5.



BARUIN ENEMA  
ROENTGENOGRAMS

---

Fig. 6. Transverse colon is stiff. No  
haustration.

---

Fig. 6.



---

Fig. 7. Same as Fig. 6, eleven months  
later.

---

Fig. 7.

Udaondo describes the various pictures seen with the procto-sigmoidoscope. These differ markedly depending on the stage of the disease and the gravity of the illness.

In an *acute case*, the mucosa of the rectum and sigmoid is hyperemic and dark red. Here and there, submucous hemorrhages are seen. These are smaller or larger and even careful instrumentation may easily cause bleeding into the bowel. In the more advanced cases the mucosa is swollen and edematous, has a violet color, and appears shiny. Later, small miliary abscesses develop which form slight elevations. These are easily confused with lymph-follicles diffusely spread throughout the diseased areas. Rupture of these abscesses brings a discharge of pus and, as a result, small shallow ulcers develop, often punctate in character. Unless one observes carefully, these can easily be overlooked. They are better recognized if the mucous surface is first cleaned by a gauze applicator.

One then observes the miliary ulcers as small red points on a background of hyperemic mucous membrane. Some ulcers may be somewhat larger but always they are shallow.

In some areas the ulcers may be confluent, resulting in a larger ulcer with irregular borders. The grayish base of these shallow lesions is covered with mucopurulent material which is removed with difficulty. The lesions are always several centimeters above the sphincter and are not found in that region. In the upper part of the rectum and the distal part of the sigmoid, we generally find the most marked involvement. The mucosa adjoining the ulcerated areas is as a rule much paler than normal or in the ulcerated segments.

In *chronic cases* which have had periods of remission and exacerbation, secondary infection often is present. One then sees shallow areas of relatively large size, (1-3 cm. in diameter-Buie) with irregular borders. These are very resistant to treatment, local as well as general.

In the *healing stage*, Udaondo noted, first a disappearance of the hyperemia. The mucosa becomes paler, the swelling subsides and ulcers gradually disappear. If this takes place slowly, small lesions may remain which later become the starting point of a subsequent exacerbation. On the other hand, in the more serious cases there is a constant tendency for the lesions to become confluent; such may cover a considerable surface of the involved area. Two cases have been reported in which the process had spread over the entire rectal mucous membrane.

#### ROENTGENOGRAPHY

In general, the symptomatology combined with procto-sigmoidoscopic and laboratory findings, will enable one to make a diagnosis of ulcerative colitis. One must, of course, remember that other conditions, as polyposis and malignant disease may display the same findings. However, a better insight into the actual disease-process calls for roentgen ray examination, inasmuch as this enables one to determine the location and spread of the lesions. This method of examination does not differentiate the lesions from those of other infections such as tuberculosis or chronic dysentery which cause similar pathological-anatomical changes, and which macroscopically resemble the ulcers of ulcerative colitis.

#### REMARKS ON TECHNIQUE

In order to make a satisfactory roentgen examination, thorough cleansing of the bowel must be carried out. In those cases with chronic obstipation, a laxative is necessary. In the others, laxatives are not used because of a possible irritation of the mucous membrane during examination. The evening before the day of examination, the patient is given a warm water enema of 1½ liters and is allowed a bowl of thin cereal for supper. The following morning nothing is given by mouth. Three hours before the examination, another warm water enema of 1½ liters is given. We may assume that in this three-hour interval between the enema and the introduction of the contrast mass, the water not expelled is completely absorbed.

As a contrast medium, we use a barium mixture, at least, when we desire a picture of the filled bowel. In those cases in which we especially wish to study the mucosa, "umbrathor" is preferred. This preparation, similar to "thordial", gives better details of mucosal conditions than do barium preparations.

Two methods of giving the contrast mass are open to us, *per os* or *per rectum*. Inasmuch as the oral method alone is not satisfactory, some observers use a combination of the two in order that a better study can be made of the upper part of the large gut.

We have been using only the rectal method. For a more exact study of the involved bowel it is advisable to control the introduction of the barium enema with the fluoroscope. In cases of ulcerative colitis, X-ray films show very marked differences depending on the stages of the illness and the chronicity of the case. Roentgenologically, therefore, one is justified in dividing the course of the illness into different stages. Knothe mentions an ulcerative, a nodular hyperplastic and a healing stage; however, at autopsy one often finds no ulceration in cases which ran a severe course. Thus, Polak Daniel reports a case in which, because of a long-standing colitis, resection of a large segment of the colon was done. The patient died immediately following the operation. At autopsy, no ulcers were found either in the resected part or in the remaining portion. It, therefore, seems wise in our opinion to add a fourth, namely, a catarrhal stage.

#### THE CATARRHAL STAGE

In the stage, in which only the superficial mucosa is affected, we do not always find on using a contrast mass that there are departures from the normal. Nevertheless, at this time the function is disturbed to a much greater degree than the pathology would indicate. The gut already manifests excessive irritability. If the rectum is involved, the barium mass may immediately be expelled by the patient unless by great effort he manages to retain it. At the time one is ready to take the picture, the rectum may be entirely empty and only the segment of the colon above the *plica rectosigmoidica* is filled with the barium. In such cases, however, the rectum may show a characteristic picture. The ampulla is narrow and enough contrast mass remains attached to the walls to enable one to see the contour and linear configurations can be made out between the folds of the markedly indurated *ampulla recti* where the barium has been retained. This irritability, which is a result of the infection of the superficial mucosa, can also manifest itself in other parts of the colon. Spasm can quickly bring about a

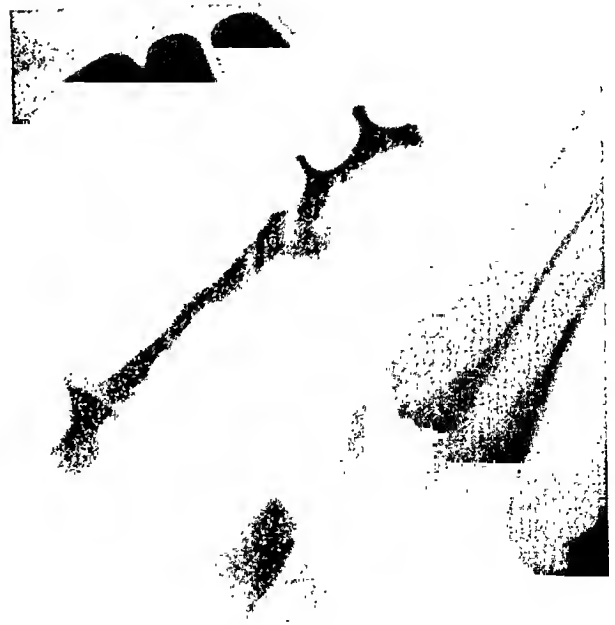
**BARUIN ENEMA  
ROENTGENOGRAMS**

Fig. 8.

---

Fig. 8. Spastic condition of colon of neurogenic origin; at autopsy intestinal wall revealed no inflammatory changes.

---



---

Fig. 9. Irregular contour. At autopsy mucosa was normal.

---

Fig. 9.

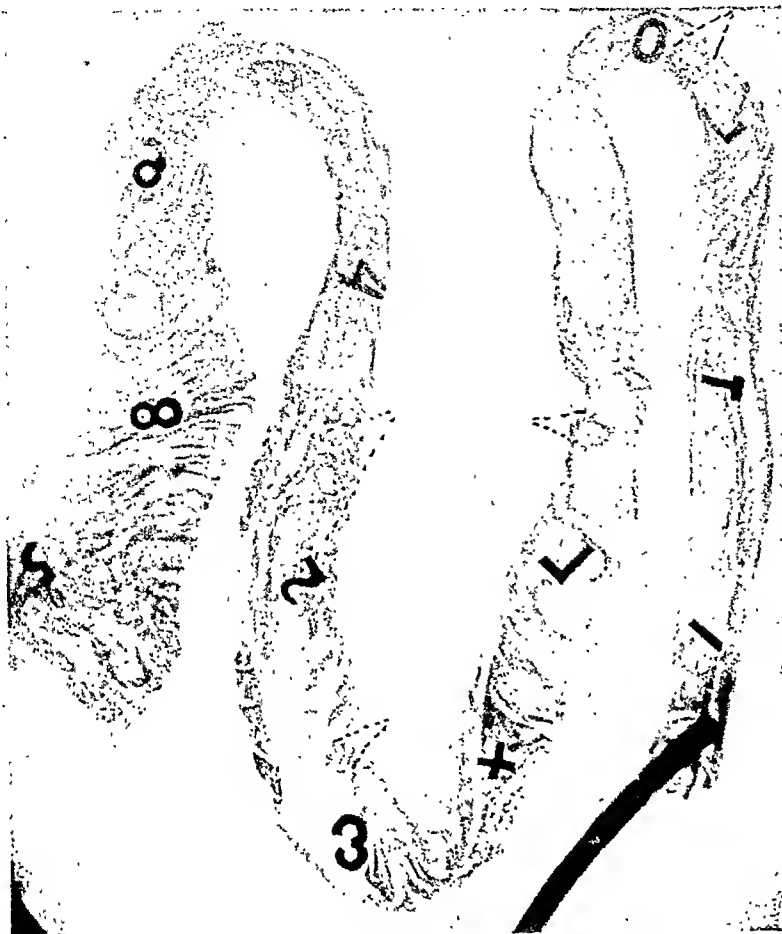


Fig. 10. X-ray film of ulcerated bowel which had been filled with umbrathor, emptied and photographed post-mortem; dotted lines indicate ulcer areas. (Figures and letters for orientation).

Fig. 10.

Fig. 11. Enlargement of a part of Fig. 10. Note particularly the ulcer indicated by dotted lines.

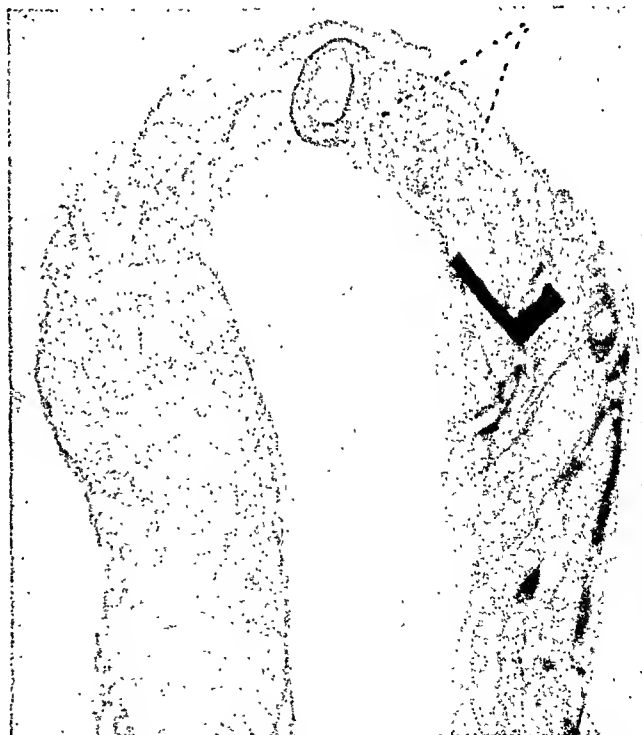


Fig. 11.



narrowing of the gut anywhere, thereby, producing the picture of a narrow band. Haustration may completely disappear, thereby, giving the bowel the form of a tube with walls evenly distant from each other. This picture is in decided contrast to that of spastic obstipation in which haustration is the characteristic feature.

The irritability of the affected portion of the gut is also responsible for the fact as described by Stierlin, that the shadow of the contrast mass in the normal segments of the bowel is much more intensive than in the diseased portion. In the otherwise normally filled colon, the affected part appears to have "dropped out." This phenomenon was originally described by Stierlin in cecum tuberculosis. In this condition, after oral administration of barium, the tuberculous cecum appeared only as a vague shadow. The explanation is that the hypermotility forces the barium through the affected part so rapidly that it does not have time to fill properly. This hypermotility has been observed in non-tuberculous states and in other portions of the bowel. The above described manifestations of irritability often are very difficult properly to evaluate. They should not be confused with the spasm that develops in any normal bowel following the introduction of the contrast mass, which spasm soon subsides. For this reason, it is important to get an idea of the character and behavior of the mucosa in the early stages of ulcerative colitis, perhaps more so than in the later stages. Knothe points to the great value which the study of an x-ray film will give early in the course of the process.

In order to accomplish this, it is necessary to evacuate the barium mass from the colon after the radiographic examination. Usually, in the catarrhal stage of ulcerative colitis this is easy because of the hypermotility of the bowel. When sufficiently empty and the intestinal walls approximate each other, enough barium remains attached to enable one to visualize the mucous folds and the spaces between them.

When we study the roentgen film we find marked changes in the contour of the intestinal folds. The longitudinal folds disappear but the transverse are more prominent. These changes are brought about by the swelling of the mucosa and the disturbed function of the *muscularis*, inasmuch as this contracts only in these areas which are not affected. Apparently the catarrhal stage may exist for a long time without necessarily causing a change for the worse. However, in those cases becoming more seriously involved, the swelling increases and the mucosal surfaces undergo a complete change. The *muscularis* is affected to such a degree that folding is no longer possible. The mucosa then forms, as it were, a series of pouches into the lumen of the gut, with crypts in between. All pliability has now been destroyed and we have a rather rigid tube-like structure which shows a honeycomb texture on the radiographic film.

#### ULCERATIVE STAGE

Knothe assumes that these crypts found in the catarrhal stage are the sites of potential ulcers. In cases where there is little or no tendency to healing, these crypts become larger and deeper and begin to ulcerate. Then we have the picture of a true ulcerative colitis. Subsequently, the deeper layers of the bowel become involved resulting in serious disturbance of function. So now we no longer have a thin

walled, pliable and elastic colon but a narrow, rather rigid tube with thick walls. Haustration and other movements are absent. At the same time, there is a tendency to shrinking and shortening, particularly of the descending and sigmoid colons. Even with complete filling these segments may remain narrow and shortened. (*Corde Colique*, Friedel). The picture described can never be mistaken and when once seen will enable one to make a correct diagnosis at once. Bargen and Weber have compared this appearance of the bowel, very fittingly, with a sclerotic blood vessel.

In this connection, however, we must consider the important part which nervous disturbances sometimes play in bringing about pictures of this kind. Repeatedly, one sees in mild cases that the roentgen picture again becomes entirely normal, which one should hardly consider possible if the roentgenologically demonstrated departures from the normal are based entirely on pathologico-anatomical changes. In this connection, let us consider the following case:

A farmer, aged twenty-three, was admitted to the Clinic at Groningen, in March, 1923. He had suffered for nine years with a persistent diarrhea, the onset of which had been rather mild. Intervals of more or less frequent diarrhea were common. Before each movement there was a painful urge, at times so severe that he had difficulty in getting to the toilet. There was much intestinal rumbling. For several months before admittance he had been growing worse. He complained of much fatigue and was greatly emaciated. A few weeks before admittance he had vomited three days in succession. The stools were generally thin and always slimy, frequently bloody, and had a foul odor. The general nutrition was poor. Pulse was within normal limits. Blood pressure 100-70. Heart and lungs normal. Outside of a little tenderness along the descending colon, the external examination of the abdomen was negative.

In the rectum, about 10 cm. from the anus, the finger met a complete stricture. This was confirmed by rectoscopy. The rectal mucosa, however, appeared quite normal and the surrounding tissue showed no induration. Radiological examinations showed the barium given by mouth to have reached the cecum in six hours. Films of the colon revealed the picture of a stiff tube without haustration. A few areas were markedly contracted. The rectal stricture was not seen.

During the first few days of his stay at the Clinic, he defecated about six to eight times daily. Diagnosis of colitis was made and appendicostomy was decided upon in order that colon irrigations might be carried out. For a long time, tannin solution (1%) was used with no improvement, so it was decided to put the entire colon at rest by instituting an artificial anus (ileostomy).

At operation, the cecum and entire colon appeared pale and felt indurated. The distal part of the cecum was also pale and rather more contracted than the remainder of the small bowel. Tannin irrigations were again instituted and the rectal stricture was stretched. Three months later the x-ray picture had not changed and the stricture was still complete. It was then decided to connect the transverse colon to the pelvic colon beyond the stricture. This attempt failed because of the rigidity and immobility of the involved bowel. In order, therefore, to restore the appendicostomy, a side to side anastomosis between the cecum and ileum was attempted. However, infection developed and death followed.

At autopsy, the small bowel revealed no abnormalities. The cecum and ascending colon were somewhat distended. The transverse colon, descending colon, and sigmoid were collapsed. There was a little thick, cloudy, yellowish fluid in the bowel. There was no narrowing at the splenic flexure or at any point below. No resistance was met at



Fig. 12.

---

Fig. 12. The gut shown in Fig. 10 opened at the site of ulcer (pathologic-anatomic preparation).

---



Fig. 13.

---

Fig. 13. Section of Fig. 12 enlarged.

---



Fig. 14. Shadows, probably haustrae taken tangentially; no ulcer.

Fig. 14.



Fig. 15. Nodular hyperplastic stage.

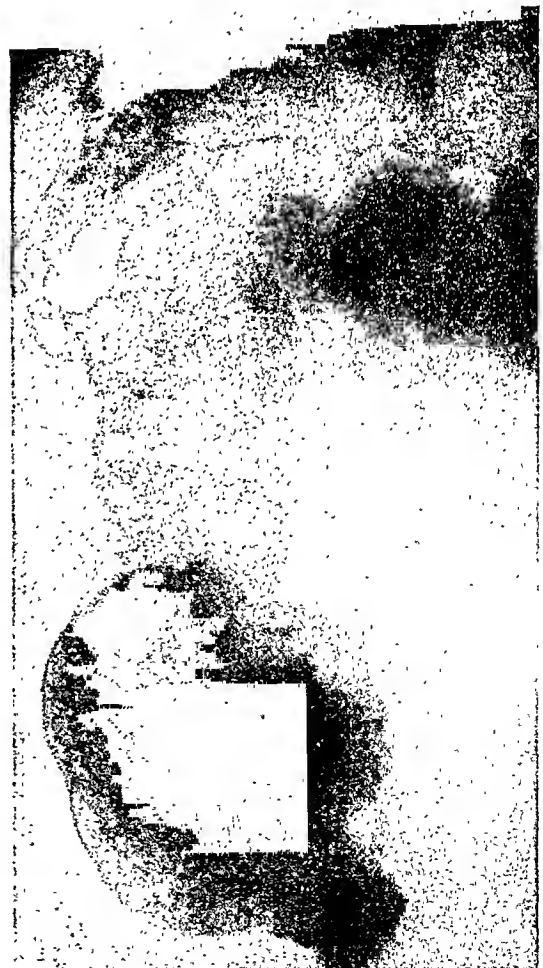


Fig. 16. Polyposis. Ascending colon and hepatic flexure.

Fig. 15.

Fig. 16.

the site of the assumed stricture. The mucosa of both colon and rectum was smooth and revealed no defects or any evidence of hyperemia. Microscopic examination made clear that the site of the clinical stenosis showed a normal intestinal wall slightly contracted in some areas. The mucosa was normal. There was no evidence anywhere of inflammation, except the peritoneal exudate found on the serous surface. The pathologist, therefore, assumed that we were dealing with a condition involving a neuropathological background.

In the film of the *ulcerated bowel*, filled with a contrast mass, the contour of the shadow differs greatly. Often it is smooth. In other instances, it may have a feathery appearance or perhaps look moth eaten. The borders may, at times, have a saw-toothed appearance. In radiographs which give one the impression of containing crypts, Bergen and Weber assume that the process is submucous. Such a case came to our attention in a patient who died two weeks after this phenomenon was observed. At autopsy no ulcers were found. Just how much ulcers are responsible for the shadow or how much the appearance is due to contraction of the *muscularis* is not clear. Sometimes a film would show a smooth contour, while on a subsequent exposure of the same case, the aspect was irregular. From the foregoing, it seems that the radiogram of the non-ulcerated bowel, as well as the ulcerated one, may show irregular borders. And inasmuch as the contour of the ulcerated gut may be perfectly smooth, it is safe to say that the film of the barium-filled bowel for the diagnosis of ulcer, is not always to be relied upon. Hence, it is necessary to rely on other roentgenological findings for determining the presence or absence of ulceration.

Regardless of whether we accept Knothe's theory about the ulcers originating in crypts or whether they were originally abscess cavities (Buie), the question arises how can we distinguish typical ulcerations on the radiograph. This problem led us to take the colon from a subject who died with a suspicion of having ulcers and treating it as we would *in vivo* in order to get a better understanding of the appearance of ulcer on the x-ray film. After this specimen was thoroughly rinsed with water, it was filled with "umbrathor." This was then poured out and a picture taken. On this film, plainly were seen circumscribed spotted areas. Some of these were surrounded by circular shadows, others by (Fig. 10 and 11) irregular shadows. On opening the gut the configuration seen on the film proved to be as far as location, form, and size was concerned, the site of ulcers (Fig. 12 and 13). The more deeply shadowed borders corresponded to the edges of the ulcers. On cutting open the entire specimen, it was found that the only ulcerated areas present, were those which we had considered as being such. However, one cannot interpret these shadows as ulcers without some reservations. Figure 14 shows the radiogram of a patient with mild obstipation. The marked areas, with rather deeply shadowed borders, are plainly seen. However, neither after introducing air nor on a film taken three weeks later were these figures seen again. Most likely they were shadows of haustra taken tangentially. If, indeed, ulcers were present they might be seen in a radiogram taken according to Fischer's method. For a correct opinion, therefore it is necessary that, after a short time has elapsed, another film be taken or that the examination be made complete by using Fischer's technique.

## THE NODULAR HYPERPLASTIC STAGE

In cases of deep ulceration which is widespread, the tendency to healing is shown by the gradual disappearance of the ulcers and the associated submucous pathology. If the radiogram is then examined, we find a nodular aspect developing. These nodules represent remnants of the remaining islands of infiltrated, swollen, and hyperplastic mucosa. (Fig. 15). Each exacerbation of ulcerative colitis should present this picture and one can, therefore, decide from the picture that the final stage is present if taken in consideration with the findings of the second or ulcerative stage. If on the other hand, the case is of many years' standing, it becomes very difficult to determine whether the condition is one of true healing or is a recurrence of the trouble. The course of the healing-process in the mucosa determines to a great extent the final condition. In the most favorable cases after many months, one finds the coarser, nodular appearances changed to a rather fine, even, speckled appearance of the entire bowel.

## THE HEALING STAGE

As healing progresses, the "nodules" become fewer, intestinal folds again appear and gradually become more visible and after a period of months the mucous membrane may again assume a normal aspect. Bergen is of the opinion that the healing stage is accompanied by the growth of new mucosal structure over the remaining "islands" of the old healing bowel. There is, however, still another possibility, that is, that the new mucosa may regenerate to the borders of the islands with the result that these may be more or less forced into the lumen of the bowel. We must bear in mind the fact that these "rests" may be the starting points of polyps which may grow to considerable size. The number of these may be great, depending on the extent and severity of the colitis. Polyposis, arising in this manner, sometimes is called "pseudopolyposis"; the roentgenogram strikingly resembles that of true polyposis.

In both, the coarse markings of the mucosal shadows are striking and haustration is absent. Both conditions may show the same irregularity of the bowel contour.

Information on the actual condition of the mucosa in these cases is not confined to a study of the intestinal folds. One can also use the *method of Fischer*, in which, after the expulsion of the contrast enema, air is introduced into the bowel and films then taken. This method requires great care because in the presence of ulcers or spasm excessive pressure immediately causes intense colic. In cases with ulceration the films now taken will reveal a rather spotted or marbled appearance of the bowel instead of that which one sees after expulsion of the barium. Sometimes the films give the impression of a braided band. The contrast mass then attached to the inner wall of the bowel resembles trellis work. (Fig. 20). Schinz points out that these spots only in part resemble shadows of ulcers. The greater number, he thinks, are shadows of the contrast mass adhering to the mucosa of the bowel wall. Schwarz and Novascinsky found, in cases coming to operation, only few ulcers in bowels showing this peculiar marbled appearance on the x-ray films. Literature on the subject warns against placing too much importance on the value of these peculiar markings in diagnosis because films of the normal colon may reveal like pictures. We have seen this

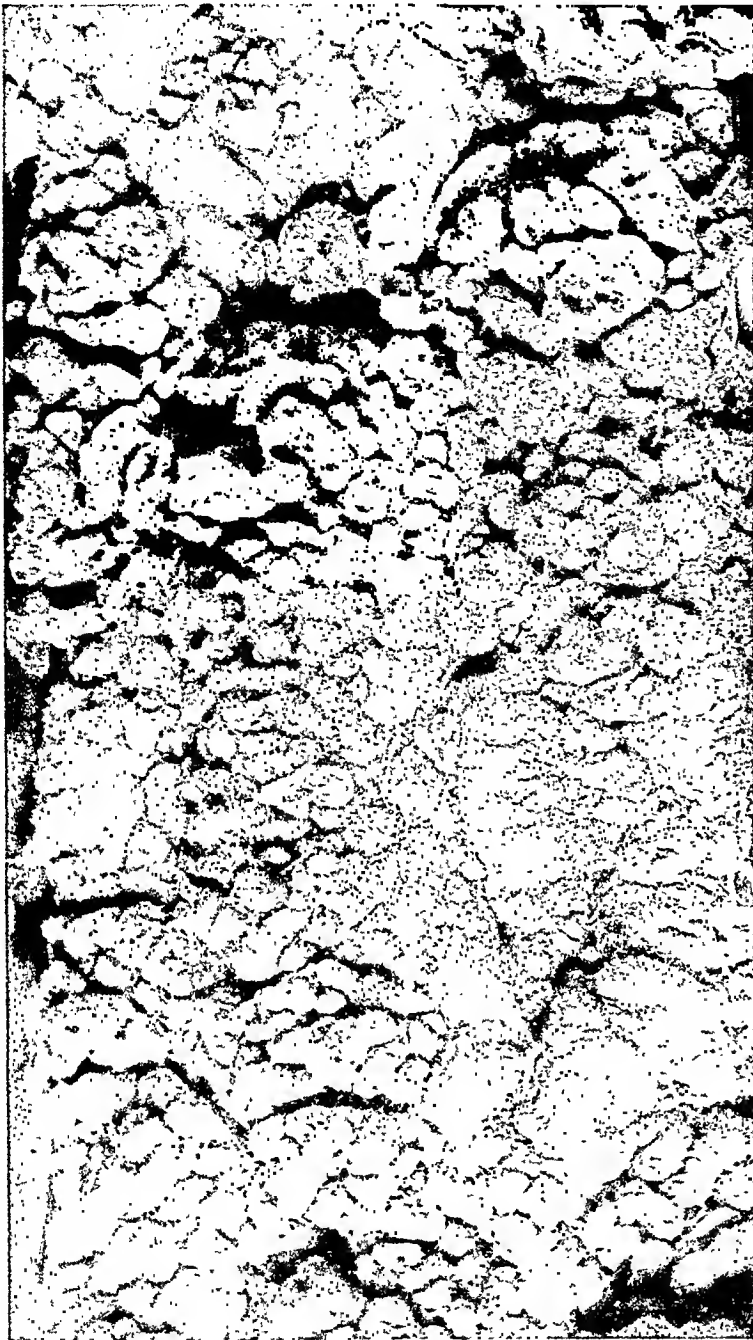


Fig. 17.

---

Fig. 17. Polyposis. (This illustration goes with Fig. 16).

---



---

Fig. 19. Pseudo-polyposis.

---



Fig. 18.

---

Fig. 18. Pseudo-polyposis (after operation).

---



Fig. 19.



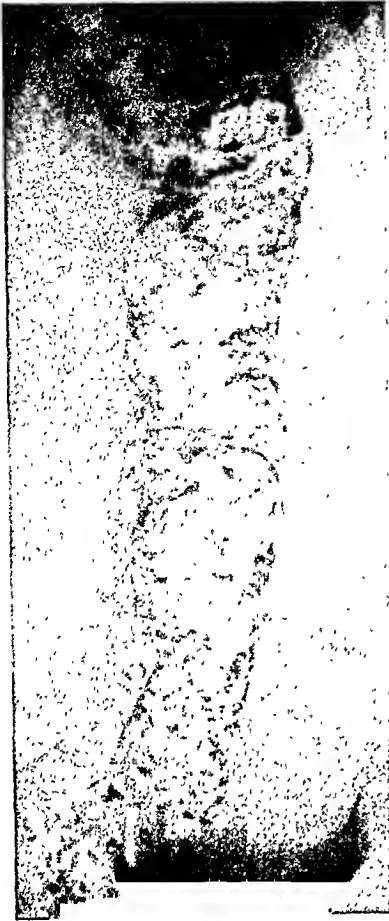


Fig. 20.



Fig. 21.

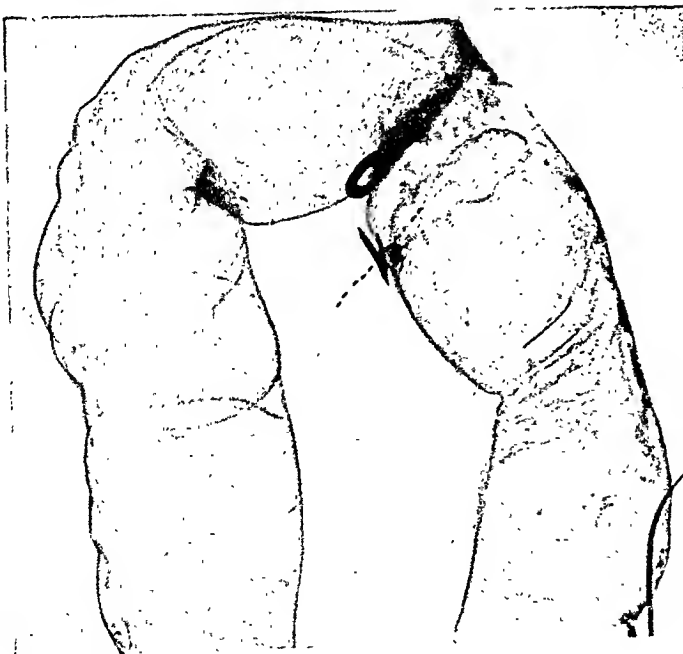


Fig. 22.

---

Fig. 20. Spotted, marbled appearance.

---



---

Fig. 21. Roentgen photo of intestine with ulcers (photo post-mortem); letters and figures for orientation (Fischer technique).

---



---

Fig. 22. Ulcers in Fig. 21 greatly enlarged.

---

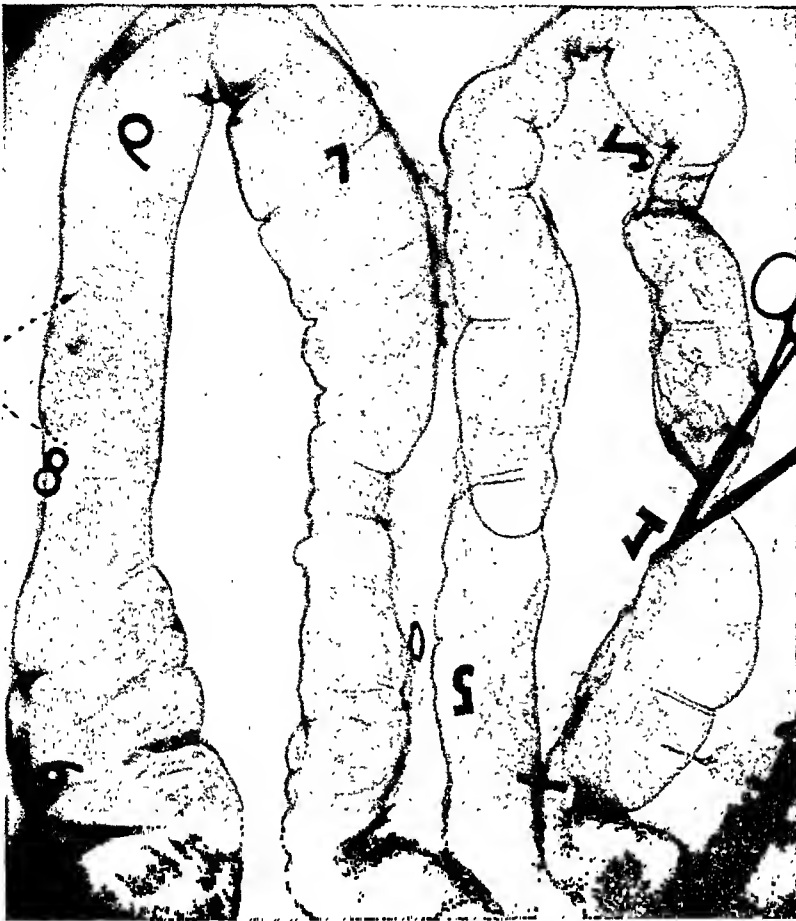


Fig. 23.

---

Fig. 23. Roentgen photo (according to Fischer) of gut with a large mucous membrane defect. Photograph post-mortem. Letters and figures for orientation.

---



Fig. 24.

---

Fig. 24. Ulceration in descending colon.

---



Fig. 25.

---

Fig. 25. Ulceration in descending colon.

---

marbled appearance in a patient who was thought to have ulcerative colitis but at autopsy not one ulcer was found in the entire colon. Apparently then, films taken by Fischer's method show nothing that is specific in the differential diagnosis of the catarrhal or the ulcerative stages of ulcerative colitis.

In order to arrive at a better understanding of this problem we undertook the application of Fischer's method to a section of the bowel from the cadaver mentioned before. After filling the gut with air, films revealed irregular figures of which the border shadows were markedly outstanding. These figures as far as localization, form and size are concerned agreed entirely with the ulcers present. In the same manner, all the existing ulcers could be recognized. Figures 21-22 will show this better than a description. There is, therefore, support for the contention that it is possible, following Fischer's method, to differentiate between true ulceration and those shadows resulting from areas of remaining contrast mass adhering to the bowel wall.

Hammer carried out analogous experiments. He used a barium combination. In many instances, he was able to recognize ulcers which were located on the borders of the shadow. However, those present on the anterior and posterior aspect, he was only occasionally able to identify, probably because of the direction of the rays. In ulcerations involving the ileocecal valve, insufficiency or even a stenosis may result. In the former, an enema of contrast material may pass through into the ileum. In the latter, a barium meal may stagnate in the small bowel. Valve insufficiency may, to a certain degree, be functional, for we have seen it occur in the catarrhal stage and on recovery found the valve again competent. Moreover, we must remember that in exceptional cases the barium enema may pass through the valve entirely in the absence of colitis.

#### LOCATION OF LESIONS IN ULCERATIVE COLITIS

As a rule, only a portion of the colon is involved in ulcerative colitis. The usual beginning localization is in the sigmoid colon and the rectum. Barger and Weber declare this is the favorite area for its development. The process may be limited to this region but may spread to any part of the colon. These observers maintain that 20% of all cases are found there. In few cases are cecum and ascending colon involved. In such, the spread is toward the hepatic flexure and the transverse colon. Wolvius and Udaondo report that in those cases with involvement of the transverse colon, pain frequently is worse at night. These patients have severe abdominal pain, palpitation, sweats, and give one the impression of being seriously ill.

#### GENERAL CONSIDERATION OF TREATMENT IN ULCERATIVE COLITIS

During the period when acute symptoms are present rest in bed is absolutely necessary. Later, with a normal temperature, when the bowel movements have dropped to one or two daily, and the contents show few or no pathological elements, the patient may gradually be allowed more freedom. A very careful regime, however, is imperative and several hours of rest should be taken daily. The x-ray findings are evidence of the fact that true healing does not always accompany a disappearance of clinical symptoms. The fact that complete restoration of the bowel may be

slow is evidenced by the experience that irrigations through a cecostomy must, in some cases, be carried out for a year. Next to physical, mental rest is of the utmost importance. The old saying that "affections of organs above the diaphragm tend to optimism and those below to pessimism" is well exemplified in ulcerative colitis. One needs, therefore, to encourage the sufferer and to put his mind at ease as far as possible. All remedies which are useful for this purpose are indicated. Weather permitting, an outdoor regime is very desirable. Sunlight and ultra-violet rays have been considered to have favorable influences. For good results, Udaondo claims it is necessary to give exposures sufficient to bring on a reaction associated with erythema and desquamation. Warm applications to the abdomen often relieve colic and are always appreciated. Electric pads can be used if desired.

#### DIETARY MANAGEMENT

From our present conception of ulcerative colitis, it is apparent that, in times past, we have been constructing our diet along too rigid lines and as a result benefits of the dietary measures hardly made up for the many complaints to which they gave rise. In recent times, we have come to realize more than ever that the colon is largely a storehouse for substances which later are expelled. It is true that in the proximal part of the large bowel some absorption takes place but the digestible substances of the food are mainly digested and absorbed in the small intestine. Rigid and arbitrary diets are not prescribed any more. Nevertheless, it is necessary to take certain precautions in feeding colitis patients.

The food taken should be such that it does not cause the least irritation of the colon. We, therefore, preferably advise food that is for the most part rather well absorbed in the small gut, leaving a minimum of residue. Vegetables containing much cellulose even when given as puree, fresh bread and fruits are not generally indicated. Boas advises a diet containing very little roughage. Udaondo is more lenient and allows, for instance, such dishes as *compotes*. Further, it is necessary that the food in question contains sufficient vitamins and has the required caloric value. The proper choice of food used in arranging the diet will generally take care of the vitamin needs. Larimore points out that the action of the vitamins in connection with the whole process must not be underestimated. If we wish to increase these, it is easily done by adding orange, tomato and grape juices. Other vitamin-rich foods can be prescribed.

In order to arrange the proper foods in an appetizing way, it is necessary that the patient take a sufficient number of calories dependent, of course, upon his body weight. For liquids, one may use boiled water to which a little cognac has been added, weak tea, cocoa, eamomile tea and small quantities of red wine. Proteins can be supplied in the early stages of the disease by using fresh fish and rare done meat. Depending upon the tolerance of the patient for different types of food these general rules can be modified. Keeping these in mind, we can later prescribe diets which we consider entirely satisfactory for the general nutrition of the patient and at the same time harmonizing with our present ideas of proper feeding in colitis.

Rankin, Barger and Buie do not favor frequent feedings in the acute stage. Their reason is that every feeding initiates peristaltic movements which may



Fig. 26.

---

Fig. 26. Large ulcer in descending  
colon.

---



Fig. 27.

---

Fig. 27. Area indicated by the dotted lines has appearance of ulcer. Post-mortem this shadow proved to be a calculus in the left kidney.

---

give rise to more frequent defecation and even to bleeding. Milk is not advised particularly when there is much diarrhea and flatulence because it is not tolerated very well and leaves considerable residue. Other milk products such as kephir, yoghurt and cheese are allowed.

Diet in the presence of obstipation will be considered presently. In those cases in which there is a tendency to diarrhea, liquid diets are more or less restricted. Schmidt and Noorden begin their treatment of acute colitis and its exacerbations by fasting the patient two days. During this time they give only weak tea and small quantities of red wine. This induces rest for the intestinal tract which usually is followed by some improvement. An acceptable diet is then prescribed. Udaondo begins dietary treatment in the acute stage by giving gruels with a little sugar, mashed potatoes, rice and macaroni. We are giving here a diet scheme which was originated by Rankin. Inasmuch as American diet and food habits differ somewhat from ours, we have made some necessary changes which make it more suitable for us in Holland or on the Continent.

Useful laxatives are magnesium sulphate ( $\frac{1}{2}$  tsp. in warm water every 15 minutes until bowels move) liquid paraffin, castor oil and senna preparations. Very frequently relief of the colon spasm is sufficient to overcome obstipation. For this purpose one could use, with satisfactory results, one of the following agents: Sulphate of atrophine subcutaneously 1 mgr. daily; tincture of belladonna, 20 or 30 drops daily; papaverine, pure .06 grams daily.

#### ORAL MEDICATION

Opium and belladonna preparations. In order to give an ulcerated bowel sufficient rest and to relieve pain in serious cases, opium and belladonna preparations must be used. Bensaude praises the use of bismuth in the form of sub-nitrate or of magisterium-bismuth. In cases with much diarrhea, he does not give the latter more than 1 gram, 4 times a day. This decreases peristaltic action while larger amounts have a laxative effect. The favorable effect of bismuth preparations is attributed to the protective and astringent effect which they have on the mucous membrane. They further are assumed to have an anti-

| BREAKFAST                         | LUNCH                             | DINNER                              |
|-----------------------------------|-----------------------------------|-------------------------------------|
| 30 grams oatmeal or other cereal  | 1 cup bouillon                    | 40 grams steamed rice               |
| 100 grams cream                   | 100 grams liver or meat           | 2 eggs or 100 grams meat or fish    |
| 30 grams bacon                    | 100 grams potatoes, two spoons    | 100 grams potatoes with gravy       |
| 1 egg                             | gravy                             | Cream pudding with fruit sauce      |
| 25 grams toast                    | 25 grams toast                    | Cup of coffee or tea with cream and |
| 20 grams butter                   | 20 grams butter                   | sugar if desired                    |
| 1 cup coffee or tea with cream or | Gelatin pudding or rice pudding   |                                     |
| sugar if desired                  | Custards and lemon pudding        |                                     |
|                                   | Coffee or tea with cream or sugar |                                     |
|                                   | if desired                        |                                     |

#### ADDITIONAL FOODS:

(1) Ripe banana, (2) Orange juice-100 grams, (3) 100 grams cream in coffee or tea, (4) Small bowl of vegetable soup, (5) A baked apple without skin, stewed apricots, pears or peaches, applesauce, (6) Small bowl tomato soup, (7) Puree of young carrots, beets, asparagus, spinach or shelled peas.

*Remarks:* These additional foods may gradually be added to the prescribed diet as soon as the condition of the patient allows. Jelly and jam are permitted. Spices and condiments are always forbidden. Fluids should not be taken while ice cold. Nothing is taken between meals in order to prevent unnecessary peristaltic movements.

#### TREATMENT OF OBSTIPATION:

If the patient is inclined to obstipation, this demands treatment inasmuch as masses of feces passing through the ulcerated area might exert a harmful influence. To combat this complication one should keep in mind rather not to use food which has any astringent action. In case diet alone does not bring desired results, one must resort to enemas or mild cathartics. Enemas should not be given with much pressure. The amount of the injected solutions should not be greater than one liter, inasmuch as the capacity of the ulcerated bowel is markedly reduced. Physiological salt solutions, liquid paraffin and camomile tea are well suited for this purpose. Solutions containing soap or glycerine, however, are not advisable because of their irritating qualities.

epic action and also to reduce the irritability of the bowel. The absorbent and anti-fermentative action of this preparation also relieves meteorism. Inasmuch as bismuth changes the reaction of sulphuretted hydrogen, it greatly reduces foetor. If stenosis is present, however, it is necessary to use care in giving bismuth for long periods of time because of its toxic effect; otherwise it can be given for long periods of time without danger.

Other absorbent remedies are sometimes used. Kaolin, animal charcoal, and norit are often useful. Astringent medicines if desired are tannin and "tannalbin"; of the latter we give from 3 to 6 grams daily. The use of astringent remedies, however, according to Udaondo, may result in a spastic type of obstipation which has a damaging influence on the inflammatory process in the colon. (Smithies employs subgallate of bismuth, a preparation readily forming a colloidal suspension—4 to 8 grams after each bowel movement) A. J. B.

Schottmüller advises *ferrum reductum*. He gives 4 to 6 grams daily. Others advise the use of gentian violet giving a 1 to 1000 solution in increasing doses of 3 to 5 up to 3 to 50 cc. daily and then gradually reducing the dose. Logan gives iodine, assuming that leukocytosis is produced. Haskell and Cantarow give calcium and para-thyroid preparations because of the finding that in ulcerative colitis the calcium content of the tissue is increased at the expense of the calcium in the blood. Cain and Lièvre treated a case of ulcera-





Fig. 28.

---

Fig. 28. Nodular hyperplastic stage.

---



---

Fig. 29. Pseudo-polypsis  
(prepared after operation).

---

Fig. 29.

tive colitis with liver extract, which resulted in rapid improvement. The clinical condition in this patient resembled that of pernicious anemia but the blood picture did not, which led them to exclude this type of anemia.

With achlorhydria, hydrochloric acid is used. The absence of pepsin in the gastric juice calls for the administration of this preparation along with the acid. Indications of any serious anemia promptly disappeared with the use of *ferrum reductum* in our cases.

#### MEDICATION PER RECTUM

Rectal medication can be given in the form of medicated clysmata, powders or suppositories. Solutions introduced in this manner should not be irritating. In order to overcome this, it is desirable to have them at body temperature. They should be preceded by a cleansing enema, the amount of which should not be over 300 cc. Enemas containing 2% boric acid solution, potassium permanganate, ichthyol, bismuth carbonate,  $\frac{1}{2}$  of 1% silver nitrate, protargol and camomile have been advised, but in most cases have been abandoned. Strong arguments against the use of some of these remedies have been advanced. In recent times much has been expected from the use of "dermatol" (5%) in oil of sesame. This is given in the evening after a cleansing enema and should be retained through the night. Other agents which have recently been used are 1% yatren (Schneck), hydrogen peroxide, tripaflavine, tannic acid 1 to 1000 and *bolus alba*. Udaondo, Centeno and Pinido advise acriflavine 1 to 4000. They give 750 cc. twice daily, this to be retained 15 to 30 minutes. After a week or two, when fever and diarrhea have subsided, it is used once daily. If improvement follows, this is then changed to 1 to 2000 solution of bicarbonate of soda and later to a 10% ichthyol solution.

In case the ulcers can be reached rectoscopically, local medication with powders may be instituted. Albu and others favor this method. Before introduction of the instrument, which must be done very carefully, it is necessary to use a cleansing enema of soda bicarbonate. The rectoscope is then introduced and medication applied directly to the ulcers. Agents frequently used for this purpose are "dermatol" 50 parts, tannic acid and sodium chloride of each 5 parts, or talcum 10 parts with "dermatol" or "xeroform" 5 parts. In case there is much tendency to bleeding, suprarenin can be added, or if severe pain is present, orthoform can be used. Preceding such treatments tincture of opium may be given *per os* in order to quiet any tendency to defecation and to favor the action of the local treatments. Such treatments should not be given oftener than every two days.

Suppositories are particularly indicated when there is inflammation in lower part of rectum frequently associated with painful tenesmus. Wolvius advises suppositories containing ichthyol 0.2, extract belladonna 0.03, dilaudid 0.003, ol. cacao 2; or balsam peru 0.150, extract hamamelis 0.030, chloret calc. 0.050. There is still to mention the treatment of Felsen who introduces oxygen into the rectum daily. In this manner he attempts to counteract the effect of organisms of decomposition.

#### OTHER METHODS OF TREATMENT

Schur advised subcutaneous injections of emetine hydrochlorate 3 times daily in doses of 0.02 grams. Intramuscularly milk and yatren casein have been

used. Rachwalsky, Bucking, Boas, Hensle and also Hulst and Hartog saw improvement with the use of blood transfusions of 300 to 500 cc. Often one transfusion was sufficient, but in other cases, two or three were necessary. Strausz was not enthusiastic about the use of transfusions as he observed cases treated in this way who developed relapses. Von Bergmann considers that ulcerative colitis may be a functional disturbance in which sensitization plays a greater or lesser role. He is not an exponent of surgical treatment and doubts very much the value of irrigations with disinfectants such as "rivanol," yatren and other substances. This hypothesis of Von Bergmann led him to advise a treatment which was used in several cases of ulcerative colitis by Kalk. These patients were at first sensitized with an intramuscular injection of horse serum. This was repeated in from 12 to 20 days. If anaphylactic shock remained absent, a third injection was given intravenously. In cases treated later, the use of horse serum was abandoned and an attempt was made to produce a chill with blood transfusions.

Von Bergmann admits that this method is not without danger inasmuch as one cannot control the severity of the reaction. He, therefore, uses a method entailing less risk. In this, the patients are given 20 cc. of horse serum intramuscularly and 12 to 20 days later a rectal enema of 200 cc. of serum. If no reaction follows, he again gives the intramuscular injection and later if necessary the intravenous injection. In many cases of serious ulcerative colitis, he declares that by using enemas of horse serum regularly the widespread ulcerated areas would absorb enough serum-albumin to cause a reaction. If successful, this happens directly after the shock. Frequently diarrhea and the production of mucous and blood cease.

However, he does not consider that the disappearance of symptoms indicates a cure but is of the opinion that the mucous membrane should now gradually restore itself. In this book "Functional Pathology" he finishes his remarks on this type of treatment with the comment that one shock treatment seldom appears to bring results and that usually relapses occur which are not so favorably influenced by the treatment after the first time.

Hurst advises therapy which is very similar to that of Von Bergmann. He gives daily intravenous injections of 40, 60, 80, or 100 cc. of polyvalent dysentery serum and considers this treatment to be a non-specific albumen reaction.

#### OPERATIVE TREATMENT

In spite of the fact that the armamentarium of the internist contains many possibilities in the attack on ulcerative colitis, one must frequently confess his inability successfully to cope with the disease and must send the patient to the surgeon. Often treatment of severe cases is not in the least successful and the patient loses ground in spite of all effort and seems doomed. In such cases one has the choice of the following surgical procedures:

1. *Appendicostomy*: In this operation the appendix is attached to the abdominal wall and opened. One is thus enabled to institute direct irrigations of the diseased bowel in the direction of peristalsis. In such cases a cannula is introduced into the rectum. The same astringents and disinfectants which are used in rectal irrigations can also be used for this purpose.

The toxic and infectious products are in this manner carried away much more satisfactorily and the ulcerated areas are reached more frequently than by rectal irrigations. A much advised method of cleansing the colon is that in which the drop method is used for a period of several hours. This solution, of course, can be medicated.

Such treatment is not very severe and for the patient the least troublesome of all surgical methods inasmuch as no intestinal contents flow into the artificial opening. It has also this advantage that it can very well be carried out at home. Against this method is the argument that the diseased intestine receives no rest which is probably the reason that this operation often does not bring the desired results.

2. *Cecostomy*: This operation can be done according to the Witzel technique or an ordinary cecal fistula can be made. In this way a portion of the intestinal contents is excreted through the wound so that the function of the diseased colon is relieved in part. Irrigations are now freely used. Schoemaker reports very favorable results with this method of treatment. The fistula can be closed off sufficiently well so that no feces escape along the drain. This is one advantage of the method.

3. *Ileostomy*: Institution of an artificial anus in the distal loop of the ileum is another surgical procedure resorted to. This operation is superior to the one just mentioned only in this respect, that the entire affected bowel is given complete rest and the passage of feces totally obviated. Here again irrigations play a large rôle in the treatment. In order to put the entire colon at rest, institution of an ileocecal anus is necessary inasmuch as one can never be positive just what part of the gut is effected. It has happened that the methods first mentioned were unsatisfactory in some cases, so eventually it became necessary to institute an artificial anus. After closure of the fistula, it is imperative to diet very carefully inasmuch as the gut has become extremely sensitive.

In a great many instances surgical treatment of such cases has brought about improvement and cure in patients who did not respond to medical treatment. The objection to operative methods is that the treatment must needs extend over a period of months or even a year or longer before the ulceration has subsided. We must also remember that the affected bowel which has not been allowed to function during this time may be shrunk or, because of adhesions of the involved areas, become stenosed so that further surgical intervention may be necessary. Regular irrigations, therefore, must be constantly carried out in cases of artificial anus in order to prevent such harmful end results.

An operative procedure which is particularly recommended by Americans is the *terminal ileostomy*. Bergen, Brown and Rankin have reported on this subject as follows: From 1921 to 1931, 82 patients with ulcerative colitis were treated in this way of which one-half died of peritonitis. Another danger associated with this method of treatment is the apparent disturbance of the water balance.

As a final refuge it is sometimes necessary to extirpate the diseased area or the entire colon. Wolvius records a case in which Michaël successfully removed the entire colon, the patient improving to such an extent that she could again carry on her work for several

years. A colon reduced to very small dimensions apparently is sufficient for proper functioning.

### VACCINE THERAPY IN THE MAYO CLINIC

Bergen succeeded in a number of patients suffering with chronic ulcerative colitis, in isolating from the intestinal ulcers a *diplo-streptococcus* which he considered the etiological factor on the basis of animal experimentation. From these diplococci, he prepared autogenous vaccines and treated his patients in this manner. From January 1, 1930, to August 1, 1931, 472 patients were treated for varying periods of time with such vaccines. In the acute stage treatment consisted of sera made of specific anti-bodies. Of this large number of patients, it appears that 352 recovered and were again able to resume their occupations.

Of the entire number: (a) 250 were symptoms free; (b) 102 showed 75% improvement; (c) 26 showed 50% improvement; (d) 45 received insufficient vaccine; (e) 49 showed no improvement.

During a period of two years, 91 patients were treated by different physicians with autogenous vaccine from the Mayo Clinic with the following results: 52 patients were symptom free; 27 were improved; 12 showed no improvement.

General as well as specific treatment was given by Bergen. In those cases, in which the ulcers could be reached with the rectoscope he applied medicated powders. In other cases, medicated enemas were administered. He also gave tincture of iodine and kaolin by mouth. The patients were allowed a general diet altho no food substances were allowed which were known to be harmful.

Bergen is of the opinion that the intestinal infection can arise from existing foci found elsewhere. For this reason he advised removal of infected teeth and diseased tonsils.

Fridkin and Gray searched for the diplococcus of Bergen in 15 cases with chronic colitis. In 12 cases this was isolated and autogenous vaccines were used. Ten of these 12 patients showed marked improvement. Three of these were seriously ill with diarrhea and intestinal bleeding when first observed. These were given small blood transfusions along with the vaccine treatment. Three patients suffered a relapse about three to four months after the termination of the vaccine therapy and bacteriological search again revealed the diplococcus of Bergen. Subsequently vaccine therapy was again successful. Kracke also feels on the basis of his investigations that the *diplo-streptococcus* of Bergen must be considered the cause of ulcerative colitis. In his opinion the treatment of the illness should consist in vaccine therapy along with general measures such as irrigations with antiseptic solutions. He gives a diet leaving very little residue. With this method of treatment he declares ileostomy infrequently necessary. Buttiaux and Sevin also acknowledge from their clinical and experimental work, the diplococcus of Bergen to be one of the causes of chronic ulcerative colitis. However, they feel that there are many other organisms instrumental in producing this affection. Among them a diplococcus isolated by themselves. They did not use vaccine therapy. Others, however, do not agree with the observers mentioned and do not ascribe much importance to Bergen's organism as a factor in this disease.

Gutierrez, Lastra and Blanco made a careful search for the diplococcus of Bergen in 16 patients with ulcer-

---

Fig. 30. Pseudo-polypoid  
(prepared after operation).

---



Fig. 30.



Fig. 31.

---

Fig. 31. Pseudo-polypoid.

---

ative colitis. Isolation and culture methods were carried out by them with great care. They found a diplococcus which resembled very much that of Bargen but in experiments on rabbits it apparently was not pathogenic. They concluded that the *diplostreptococcus* was not the cause of ulcerative colitis.

Vaccine therapy was not used by them. Rafsky and Manheim also deny the etiological importance of Bargen's diplococcus in ulcerative colitis. On the basis of a large number of investigations carried out on pati-

ents as well as on normal individuals, they believe that the diplococcus is not found in all cases of ulcerative colitis and furthermore is sometimes found in the normal intestine. They did not use vaccine therapy.

The unusually favorable results following the use of auto-vaccines which Bargen and some other clinicians noted in a large percentage of their patients suffering with ulcerative colitis led us to institute that type of treatment in the patients of the Groningen Clinic.

(To be continued in May issue, Vol. 11, No. 3).

## Unrecognized "Strokes" and the Gastro-Enterologist\*

By

WALTER C. ALVAREZ, M.D.  
ROCHESTER, MINNESOTA

**R**ECENTLY, while reading the memoirs of Ike Hoover, for years head usher at the White House, I was impressed with the great medical significance of what he has to say about the beginnings of President Wilson's final illness.

He tells of a few days in Paris when Wilson remained in his room with what was thought to be a slight cold. Soon he was up and back to work as usual, and to the eyes even of a physician, he might well have seemed to be the same robust, healthy man. But to the keen-eyed usher who worked beside him for fourteen hours a day, watching his contacts with the outside world, it was apparent that a great change had come. The master who had always been kindly, and friendly, and thoughtful for the comfort of those about him was now austere and distant and suspicious. He kept complaining that the house was full of French spies, and he became fussy and niggardly over little things. In the light of what happened later, it seems obvious that he had suffered the first of that series of strokes which was to influence profoundly the course of civilization.

If, as might well have happened, the President had wakened with some nausea and dizziness, and had vomited, or if he had complained of a toxic feeling, it is easy to see how a gastro-enterologist might have been called in, and how he might have blamed the state dinner of the evening before, or the shrimps, or the cheese, or the pressure of worry and overwork. And, even if Ike Hoover's observations and worries had been communicated to a neurologist, might he too not have looked up, after failing to find any sign of weakened muscles or altered reflexes, and expressed his opinion that all was well?

### *The need for asking about changes in character*

The point I wish to stress is that in many cases the physician who sees the patient after his first thrombosis is almost certain to miss the correct diagnosis, because all he hears about is an upset stomach. The changes in personality which sometimes follow are usually noticed by the family but are seldom mentioned to the physician unless he asks about them. The reason seems to be that everyone assumes that

the mental upset will disappear as soon as the indigestion is straightened out.

The home physician, who knew the man as he was before the attack of "acute indigestion," may recognize some of these changes when they appear, but he too tends to look on them as secondary to disease in abdomen or thorax. When the patient is depressed and apathetic, everyone usually agrees on one point, and this is that he should "snap out of it."

In these cases the consultant is even more likely to make mistakes than is the family physician, because he never saw the man before and cannot realize how big an injury has been wrought in the brain. Actually, the acquaintance of the medical profession with this syndrome seems to be so slight that sometimes the physicians in charge of the patient will refuse to accept the diagnosis of a mild stroke even when this is urged on them. Sometimes even the second mild "stroke," such as Wilson apparently suffered at Wichita, is looked on as a collapse due to overwork, and it is only when the big one comes, with weakness of hand or foot, or uncertainty of speech, that the true state of affairs becomes obvious.

### *A stroke can take place without any sign of shock, and without any great change in character*

The diagnosis of the first of a series of cerebral injuries is even more difficult when it takes place during sleep and the patient wakes feeling about as well as usual. To show what I mean, a very intelligent man, rose from his bed one morning to find that his unusually good memory was largely gone. His home physician refused to become concerned about this, and as so commonly happens when we medical men do not understand something, he questioned the actuality of the occurrence. A few months later, while sitting quietly at dinner, the patient suddenly felt a curious sensation in one cheek and soon found that that side of his face was anesthetic. To me the remarkable fact is that, at the time, there wasn't a trace of dizziness or headache. Careful examination by the neurologists at the Mayo Clinic left little doubt about the presence of arteriosclerotic injuries to the brain.

We see, then, that a small part of the brain can suddenly be destroyed without the production of any shock. Under the circumstances, it must be that many

of the nervous breakdowns and curious, poorly explained gastro-intestinal syndromes which we physicians see in persons past forty-five must have begun with one of these unrecognizable "strokes."

If the man whose experience I have just described had not been able to present an anesthetic cheek, he would have continued to get little sympathy from his medical advisers, and later, when perhaps he began to go to pieces mentally and physically, he might have had to part uselessly with teeth and tonsils and appendix.

#### *Some arteriosclerotics die slowly at the top*

As Janeway pointed out years ago, there are several ways in which a patient with hypertension can end up: he can die a heart death or a kidney death, or he can die by inches, "at the top." This may be well known academically, but years of consultant practice has impressed me with the fact that the opening scenes in the drama are seldom recognized for what they are. Actually, a few years ago when I wrote a description of these phenomena as I have observed them, an editor with large clinical experience refused to publish it because he thought such things were too rare to be worth talking about. But curiously, when I turned for comfort to my friend, James Kernohan, whose experience in the field of brain pathology is enormous, he remarked that he rarely showed such brains at clinico-pathologic conferences because, in the first place, they are too commonly met with to interest him any more, and in the second place, he is so often disappointed when he searches the record for the expected history of repeated short upsets with changes in personality. Too often it is apparent from the history sheet that the character of the symptoms caused the attending physicians to spend all their time hunting for the cause of the disease in thorax and abdomen.

#### SOME TYPICAL CASES

The following cases, reported briefly, will bring out some of the points I wish to make:

*Case 1.*—A woman, aged sixty-five, always active mentally and physically and proud of a host of friends, suddenly, while undressing for bed, felt a "heat wave" strike through the abdomen. Ever since then she has "felt terrible" and has been a sore problem to herself and to her daughter who looks after her.

Only careful questioning revealed the fact that for a few days after the first shock there was a slight defect in the swallowing mechanism. At the time the resultant cough was thought to be due to some infection in the throat, and it was treated in the usual way with gargles and sprays. Because the first distress was felt in the abdomen, her physicians, one after another, kept studying the digestive tract and piling up a stack of roentgenograms. As was to be expected, no one was able to find anything definite, or to help her in the slightest.

To me the outstanding feature of the case was the nervous breakdown, with its sudden onset. Two years after the first shock, when I first saw her, her complaints were the same as they were at the beginning of the illness.

*Case 2.*—Another patient, also an energetic, public-spirited, and intelligent woman who had enjoyed perfect digestion during all of her sixty years of life, awakened one morning nauseated and with the "room spinning around." The physicians who saw her were so impressed by the vomiting that they then and thereafter assumed that the trouble must be in the digestive tract. I saw her because they feared, on doubtful roentgenographic evidence, that she must be suffering with carcinoma of the colon. When

she came to this Clinic for operation, the carcinoma could not be found. Because the opening scene in the drama was so typical of a stroke, I promptly asked her, and soon obtained, a *story of a marked change in personality*, with loss of memory and of all previous interests. These troubles have persisted now for over two years, as I warned the family they would.

Incidentally one of the important things about making the proper diagnosis in these cases is that it saves the physician from giving a good prognosis and promising a cure. Such a mistake can only hurt his reputation and the cause of scientific medicine.

*Case 3.*—Another woman, aged about sixty-five, was seen by me with Dr. Wakefield. She had always had perfect digestion until one morning when, while getting breakfast, she suddenly became confused and for the next three hours kept asking her husband over and over again what had happened. Her home physicians, who apparently failed to inquire about the mode of onset of the trouble, kept looking on her problem as a purely gastro-intestinal one because all the history they obtained was to the effect that whenever she ate she was so upset that she vowed she would not eat again. The putting of any food into the stomach immediately brought on several types of distress which I believe are due to a great exaggeration of those reflexes which normally arise in the active digestive tract, and which, in some overly sensitive persons, bring flushing, excessive perspiration, or a feeling of warmth, or of sinking, or depression, or utter exhaustion.

Fortunately, in this case, the gastro-intestinal disturbances largely disappeared during the course of a year, leaving only the childishness and the loss of memory which, although a source of concern to the husband, were not mentioned by him until I asked him about them.

The next case illustrates the mistake of treating an unimportant disease:

*Case 4.*—A university president, past middle age, overworked and harassed by hostile politicians, awakened one morning with an attack of "acute indigestion." Internists in his city found a moderate hypertension, and, unfortunately, a few cysts of *Endameba histolytica* in the stools. When a strenuous course of treatment in a hospital failed to dislodge all of the amebas, the physicians wanted to attack them again, but, fortunately, the family doctor had been keeping his eyes open; he did not know much about amebas, but after years of contact with the sick he could often see the hand of death on a man's shoulder before it was visible to others. When he communicated his fears to me I backed him up, and when two months later death came to the patient after a second, larger stroke, we were glad that the tired man had been spared the annoyance of more exhausting and futile treatments.

I speak humbly of such mistakes because, as I look back over the earlier years of my practice, I can now see where sometimes I failed not only to recognize the nature of the opening scene in these dramas but I was none too sure at the *dénouement*. I know also that I must be missing the correct diagnosis in a number of these cases seen today, sometimes because I do not get all of the important history from the patient, and sometimes because I do not get enough information from the family.

The next is a case in which for a long time some doubt existed as to the diagnosis:

*Case 5.*—In January, 1920, I saw a business executive, aged fifty-three, who complained of nervousness, mental depression, spells of apprehension, and weakness of vision so that he could not read for more than a few minutes at a time. In addition, he complained of heartburn, occasional palpitation, and worst of all, of feelings of great exhaustion after eating. He expected me, as a gastro-enterologist, to cure him.



He had been strong and active until four months before I saw him, when, after overdoing at golf, he went to bed for three days with an unexplained fever. A few days before I saw him he had another similar but milder attack, again after allowing himself to become exhausted on the links. The curious thing was that after this mild indisposition, he never rallied, and for the next five and a half years, he was hardly able to answer his mail.

Many examinations failed to show anything physically wrong besides a mild hypertension and arteriosclerosis. Sometimes he complained of his stomach, and sometimes he was much concerned about his heart, but always his head did not feel right; he never could read or do much work, and at times he had dizzy spells.

After a year or so, when he came to know me better, he admitted that he had had similar sudden "nervous breakdowns" in 1902, 1909, and 1910, but then each time he was able to recover. He did not care to talk about these episodes because his father and older sister had both died after a series of apoplectic attacks.

In this case, the man looked well and kept well-groomed until the day of his death. The outstanding feature of the illness was the "nervous breakdown." Because this was ushered in by a series of short and apparently unimportant illnesses, and because it remained unchanged until he died, with what was probably a "stroke," I think the logical explanation is that the brain suffered a series of vascular injuries. Unfortunately, a necropsy was not obtained.

#### *One has to live close to a disease to understand it well*

I have often been impressed by the fact that the only way in which a physician can learn the fine points of a disease, and can come to understand and sympathize deeply with the sufferings of the victim and his family, is either to experience the illness himself or else to see its unfoldings in one of his relatives or close friends. Then he learns that many of the most important and troublesome symptoms, together with their repercussions on the family, do not appear on the history even when it is taken by an able clinician.

My best teachers in this field of medicine were, unfortunately, two of my closest friends, a man and his wife whom I had to watch as they died by inches in the course of several years. In the case of the husband, as so commonly happens, the first upsets were not recognized for what they were. The diagnosis began to be clear only when one of the attacks of anxiety about the heart, with a gassy stomach, was followed by violent spells of coughing due to a partial loss of the reflexes which serve to keep food out of the larynx. Later, another spell was associated with a transient weakness of the muscles of one leg, and then it became obvious that this man, long known to have hypertension, was doomed to die a cerebral death.

With each attack more of the brain was destroyed, until after two years he became so crippled mentally that he had to retire from his business. He who had been wide-awake and well-groomed, an able college president and a brilliant lecturer; a friendly man, with a host of friends, became slow and irritable and despondent, and so careless about his appearance that friends suspected him of using drugs. After two more years of suffering, with the attendant wrecking of the nerves of his wife, death came to bring him his release.

Eventually it dawned on me that some of the short illnesses that had puzzled us during the first year of this man's mental deterioration must have been due to small injuries to the brain similar to the larger ones that came later. The family and I were able then to

trace the beginnings of the disease back to a short, hitherto poorly-understood, illness that came while the patient was on a trip to the Orient. We at last understood why a man who had always been a most devoted and loving husband and a good correspondent had not written home for months at a time. When, at the time, his wife spoke to me about this, I must admit that the important medical significance of the fact was not fully grasped; in many men such behavior would not excite comment, but in this man, with his previous good record, I should have seen that this neglect was decidedly pathologic, and the first sign of a big change in personality.

Later, when the wife's troubles began, they were easier to understand, because her first thrombosis was large enough to injure the centers for speech and for the arm and leg. After recovering from this shock, she had the misfortune to live on for some six years, hoping first for recovery, and later for death. No one who has not lived close to such a patient can realize the agony of suffering that is experienced by those whose brain, the center of thought and perception, has been badly injured. I have often begged highly intelligent persons with such injuries to describe their sufferings, but it seems to be impossible for them; all they can say is that "it is awful." Perhaps it is like trying to describe an odor so that someone else can recognize it.

Even when I knew what was doubtless happening in the brain of my friend, it was hard at times to realize that a sudden attack of "acute indigestion," or of "biliousness" with vertigo, must be due to a fresh injury to the brain and not to disease in some part of the digestive tract. There is no question that some of these attacks, seen by themselves without the rest of the picture, could easily have deceived a good gastro-enterologist. That, actually, they were not due to any form of indigestion was shown by the fact, first, that before this illness the patient had always enjoyed a "cast iron stomach"; second, that the attacks came suddenly at any time of the day or night; and, finally, that at necropsy the abdomen and its contents were normal. It was the brain that was diseased, and, as was to be expected, it was easy to find the large areas of softening due to the first and the last big thromboses, with, in between, dozens of specks due to smaller injuries.

Curiously, this last patient, in spite of the aphasic and the repeated and extensive injuries to the brain, showed very little change in personality. Almost until the end she kept her keen intelligence, her wide interests, her sense of humor, and her devotion to family and friends and work.

#### SUMMARY

"Acute indigestion" in an elderly person may well be due to an unrecognized stroke. Especially when the patient goes on complaining, the physician should take note, first, of the sudden onset, and second, of changes in character with loss of memory and interests, and often of the ability to work.

Small strokes may go unrecognized because they take place during sleep or because they are not accompanied by symptoms of shock. Typical cases are described.

After a "stroke," the digestive tract may perhaps become spastic, much as an injured arm or leg is spastic, or "storms" may go down the vagus nerve, much as they do in migraine.

# Liver Function in Hepatic and Extrahepatic Diseases\*

## 1. The Results of Clinical Experience with 326 Cases

By

G. K. WEVER, M.D.  
T. L. ALTHAUSEN, M.D.  
G. R. BISKIND, M.D.

and

WM. J. KERR, M.D.  
SAN FRANCISCO, CALIFORNIA

THE present report is the outgrowth of seven years of clinical and laboratory studies in hepatic function on patients with and without diseases of the liver, rather than the results of a comparative study of liver function tests. During this time, in an effort to obtain better insight into the patient's condition, most of the common and some of the less common liver function tests were used, the choice in individual cases depending on the promise of useful information to be obtained from any particular test under the given circumstances. The extent to which hepatic function may be influenced by extrahepatic diseases was the object of special interest and for this reason about half of the patients in this series had no direct involvement of the liver. Since among the different liver function tests only three, the Rose Bengal dye excretion test (1), the modified dextrose tolerance test (2), and the icterus index (3), were performed in a sufficient number of patients to justify definite conclusions, our report is limited to these tests.

The *Rose Bengal test* depends upon the ability of the liver to eliminate certain foreign substances from the blood-stream. The technic of this test, as used by us, was described in 1927 (1). An improvement by which the samples of plasma are compared in a spectroscope instead of a colorimeter, was introduced in 1931 (4) and utilized thereafter. The upper limit of normal for the spectroscopic method has been accepted as 55 per cent of the standard at the end of 8 minutes, and 35 per cent of the standard at the end of 16 minutes. These limits are 5 per cent lower with the colorimetric method, and this correction was added to the readings obtained prior to 1931. In instances where the specimens at 8 and 16 minutes gave inconsistent results, the latter was considered more significant. For convenience, the results of the Rose Bengal test were classified according to the degree of retention. Tests showing a retention of from 55 to 65 per cent in 8 minutes, and from 35 to 45 per cent in 16 minutes, were considered as slightly positive; those from 66 to 75 per cent and from 46 to 55 per cent respectively, as moderately positive; and those in excess of 75 and 55 per cent, as markedly positive. In classifying the results of the test, the reading at 16 minutes was again considered the more important. The Rose Bengal test was performed, often repeatedly, in 302 patients.

The *modified glucose tolerance test*, designed as a test of one of the metabolic functions of the liver, depends on the ability of this organ to maintain the blood-sugar at a certain level following the administration of insulin, dextrose, and water. At the time of the first report on this test the dividing-line between normal and abnormal function was empirically placed in the vicinity of 70 mg. per cent. In view of further experience the outcome of the test will, in this paper, be considered abnormal if the blood-sugar drops to 65 mg. per cent or lower during the test. A second criterion, applicable chiefly in borderline cases, or when the patient has an unusually low or high fasting blood-sugar, is the difference between the initial and the lowest blood-sugar during the test. In normal individuals, this difference rarely exceeds 30 mg. per cent, while in patients with impaired hepatic function it is usually higher, and may exceed 70 mg. per cent. This is merely another way of judging the ability of the liver to maintain a fairly constant blood-sugar level under the conditions of the test. Determinations of the blood-sugar were made by the method of Folin and Wu (5). Methods which exclude the non-carbohydrate reducing substances of the blood may not give comparable results. A total of 123 patients were studied by this test.

The *icterus index* was determined once or more often in 119 patients, chiefly in those with direct involvement of the liver.

Our patients have been divided into three main groups. The first comprises 106 patients with intrinsic diseases of the liver (Table I). Patients in the second group, numbering 49, had neoplasms of the liver and diseases of the malignant lymphoma type (Table V). There are considered to be invasions of the liver because without any intrinsic disease of hepatic cells, there is a destructive process involving this organ. The third group consists of 170 patients with diseases of extrahepatic nature (Table VII). Except in six instances, all our patients were ill enough to be in hospital.

### A. INTRINSIC DISEASES OF THE LIVER

#### 1. ACUTE HEPATITIS (TABLE II)

a. "*Catarrhal jaundice*." The excretory function of the liver was found to be markedly impaired in these patients during the acute stage of the disease, but to recover later. Jolliffe (6), who used the bromsulphalein test, found that normal excretion was re-established about two weeks after the height of jaundice. In our case No. 14, the Rose Bengal test became

\*From the Department of Medicine and Department of Pathology of the University of California Medical School, San Francisco. Submitted January 3, 1935.

TABLE I  
*Intrinsic Diseases of the Liver*

|                           | No.<br>of<br>Cases | Neg. | Rose Bengal Test |        |      |                    | Modified Glucose<br>Tolerance Test |      |                    |              | Comparison of the Two Tests |                                |                                |        |
|---------------------------|--------------------|------|------------------|--------|------|--------------------|------------------------------------|------|--------------------|--------------|-----------------------------|--------------------------------|--------------------------------|--------|
|                           |                    |      | Positive         |        |      | No.<br>of<br>Cases | Neg.                               | Pos. | No.<br>of<br>Cases | Both<br>pos. | Both<br>neg.                | R.B.<br>pos.<br>M.G.T.<br>neg. | R.B.<br>neg.<br>M.G.T.<br>pos. |        |
|                           |                    |      | No.              | Slight | Mod. |                    |                                    |      |                    |              |                             |                                |                                | Marked |
| Catarrhal jaundice        | 12                 | 3    | 9                | 1      | 1    | 7                  | 6                                  | 0    | 6                  | 4            | 2                           |                                |                                |        |
| Arsphenamine hepatitis    | 6                  | 0    | 6                | 3      | 1    | 2                  | 5                                  | 1    | 4                  | 4            | 3                           |                                |                                |        |
| Toxic hepatitis           | 3                  | 0    | 3                | 1      | 0    | 2                  | 2                                  | 0    | 2                  | 2            |                             |                                | 1                              | 2      |
| Portal cirrhosis          | 33                 | 1    | 32               | 4      | 8    | 20                 | 13                                 | 5    | 8                  | 13           | 7                           |                                |                                |        |
| Biliary cirrhosis         | 10                 | 0    | 10               | 1      | 3    | 6                  | 5                                  | 0    | 5                  | 4            | 4                           |                                | 5                              | 1      |
| Banti's disease           | 7                  | 0    | 7                | 0      | 3    | 4                  | 2                                  | 0    | 2                  | 2            | 2                           |                                |                                |        |
| Hemochromatosis           | 5                  | 1    | 4                | 2      | 2    | 0                  | 3                                  | 0    | 1                  | 1            | 1                           |                                |                                |        |
| Toxic cirrhosis           | 3                  | 0    | 3                | 0      | 0    | 3                  | 3                                  | 2    | 1                  | 2            | 1                           |                                | 1                              |        |
| Chronic lues of the liver | 8                  | 1    | 7                | 3      | 3    | 1                  | 1                                  | 0    | 1                  | 1            | 1                           |                                |                                |        |
| Infections of the liver   | 4                  | 1    | 3                | 2      | 0    | 1                  | 3                                  | 0    | 3                  | 3            | 3                           |                                |                                |        |
| Hepatomegaly              | 10                 | 3    | 7                | 3      | 2    | 2                  | 5                                  | 1    | 4                  | 5            | 3                           |                                | 1                              | 1      |
| Total                     | 101                | 10   | 91               | 20     | 23   | 48                 | 46                                 | 9    | 37                 | 41           | 29                          |                                | 8                              | 4      |

normal while the icterus index was still 70. This is probably not an infrequent occurrence during convalescence, and indicates that quantities of bilirubin which have been stored in the tissues are being transported by the blood stream to the liver for excretion. If dye excretion remains impaired for several months after the jaundice clears up, the suspicion should be aroused that the patient had an attack of sub-acute yellow atrophy of the liver, and may be a candidate for toxic cirrhosis of the liver (Case No. 1). This is particularly likely if the attacks of jaundice recur.

The modified glucose tolerance test may continue to produce abnormally low minimum blood sugars for a time after the excretion of Rose Bengal returns to normal. From experiments on animals (7) this can probably be explained by increased utilization of sugar due mainly to hyperactivity of newly regenerated hepatic parenchyma. Possible additional factors are compensatory mechanisms in the pancreas and the muscles. When once established, they may not recede with the same rapidity with which regeneration of the liver takes place.

b. *Arsphenamine hepatitis.* Jaundice in the course of arsenical therapy of syphilis was usually accompanied by considerable impairment of hepatic function. After administration of arsphenamine was discontinued, repetition of the Rose Bengal test at intervals showed gradual improvement which, in most cases, ended in re-establishment of a normal excretory function. As was pointed out by Biskind, Epstein and Kerr (8), further administration of arsenicals should be guided by the outcome of one or more liver function tests.

c. *Toxic hepatitis.* One or more tests of hepatic function were positive in every patient of this small group. The results of successive tests on patient No. 22, with arsenical poisoning, throw interesting light on the mechanism of impairment of the excretory and metabolic functions of the liver. During the acute stage of the illness, when the patient's liver was enlarged, presumably due to necrosis and swelling of its parenchyma, there was marked impairment of the metabolic function, as measured by the modified glucose tolerance and the galactose tolerance tests. At the same time, dye excretion was normal, as shown by repeated tests, indicating that there was no interference with the biliary channels or with the permeability of hepatic cells. As parenchymatous regeneration took place it was reflected in progressive improvement of the metabolic function. In contrast to this, the excretion of the Rose Bengal dye became impaired. As

previously reported by Althausen (9), lack of connection between the new hepatic cells and the bile ducts was probably the main cause of this phenomenon, but mechanical interference with bile passages incident to shrinkage of the liver may have been a contributing factor.

## 2. CHRONIC HEPATITIS (TABLE III)

a. *Cirrhosis of the liver.* Our group of 60 patients with different types of cirrhosis of the liver were clinically characterized by hepatomegaly in 52 cases, splenomegaly in 27 cases, ascites in 30 cases, and clinical evidence of a collateral circulation in 23 cases. In this disease the Rose Bengal test is at its best, for few are the exceptions to the rule that normal results with this test practically eliminate the diagnosis of cirrhosis of the liver. Rao (10) made essentially similar observations with this test in his cases of hepatic cirrhosis.

The modified glucose tolerance test was positive with equal frequency in biliary cirrhosis. This test is, however, less reliable in atrophic cirrhosis, and is usually negative in Mallory's (11) toxic cirrhosis, which is clinically often indistinguishable from the atrophic type. The reason for this is massive regeneration of hepatic tissue in toxic cirrhosis (9) which permits normal metabolic function.

From a comparison of the icterus index with the degree of Rose Bengal retention in hepatic cirrhosis, we see a rough correlation between the two until the icterus index reaches 30 units (Table IV). Above this point, the icterus index does not indicate greater hepatic damage, as measured by the Rose Bengal test. This correlation holds only for the group as a whole, and does not mean that the dye excretion test can be replaced by estimations of serum bilirubin.

Since patients without ascites are presumably in an earlier stage of cirrhosis, it is interesting to note that the average Rose Bengal readings for 8 and 16 minutes, as well as the average icterus index, of this group were lower than those of patients with ascites.

b. *Chronic syphilis of the liver* (Table I). Hepatic function, as measured by our tests, is considerably impaired in this disease. Repeated liver function tests (up to 6 in the same patient) indicated that antiluec therapy continued over many months brought about improvement in function. This subject has been discussed in detail elsewhere (8).

A patient in this group on whom splenectomy was performed showed a temporary increase in dye retention until remaining portions of the reticuloendothel-

ial system compensated for the loss of the spleen. Similar observations on the rôle of the spleen in the removal of Rose Bengal from the blood stream were made by Dieryck (12) on splenectomized rabbits.

c. *Pyogenic and parasitic infections of the liver.* (Table I). Two patients with cholangitis gave a positive response to both tests of hepatic function. One of these patients was re-examined by the Rose Bengal test after the infection had subsided clinically, and at that time dye excretion was normal.

One patient was examined by the Rose Bengal and modified glucose tolerance tests two years after the excision of a large echinococcus cyst from the liver. At that time he had a large mass attached to the liver which was interpreted as a recurrence of his disease. Both tests were positive. Two and a half years later the mass had disappeared and the Rose Bengal test had become negative.

One patient with an amebic abscess of the liver had normal excretion of Rose Bengal.

### 3. HEPATOMEGALY

One or both hepatic function tests were performed in ten patients with hepatomegaly of undetermined origin and without other clinical evidence of hepatic disease. The results are given in Table I.

## B. NEOPLASMS OF THE LIVER

### 1. CARCINOMA

The two patients with primary neoplasms, and three out of every four patients with secondary malignancies of the liver, had positive Rose Bengal tests (Table V). The site of the primary tumor influenced the outcome of this test in the sense that metastases from near organs were more apt to cause abnormal dye retention than those from distant organs. For example, all gastric and pancreatic carcinomata in this series gave positive tests. This finding was probably due to the fact that metastases from neighboring organs have an opportunity to become more widespread by the time the primary tumor causes the patient to seek medical aid.

A comparison of the icterus index with the degree of Rose Bengal retention (Table VI) shows that the two are parallel. In addition, the bilirubinemia for the same degree of dye retention is seen to be proportionately much greater in neoplasms than in cirrhosis of the liver (compare Tables IV and VI). This suggests that, in many cases of metastatic carcinoma of the liver, it is mechanical obstruction rather than actual destruction of hepatic tissue that interferes with excretion of the dye. Such a view is supported by the

TABLE II  
*Acute Hepatitis*

|                                  | Case No. | Hepato-<br>megaly | Spleno-<br>megaly | Uro-<br>bilin-<br>uria* | Icterus<br>Index | Rose<br>8 min. | Bengal<br>16 min. | M. G. T. |      | Remarks                                                              |
|----------------------------------|----------|-------------------|-------------------|-------------------------|------------------|----------------|-------------------|----------|------|----------------------------------------------------------------------|
|                                  |          |                   |                   |                         |                  |                |                   | Low      | Dif. |                                                                      |
| a. <i>Catarrhal Jaundice</i>     | 1        | +                 | 0                 |                         | 8                | 79             | 48                | 54       | 47   | 3 mon. after onset. Cholecystography normal.                         |
|                                  | 2        | +                 | +                 |                         | 36               | 100            | 100               |          |      |                                                                      |
|                                  | 3        | +                 | +                 | 2+                      | 75               | 100            | 87                | 48       | 46   |                                                                      |
|                                  | 4        | 0                 | 0                 |                         | 40               |                |                   | 42       | 33   | Moderate ascites.                                                    |
|                                  | 5a       | 0                 | 0                 | +                       | 105              | 80             | 60                |          |      |                                                                      |
|                                  | 5b       | 0                 | 0                 |                         | 8                | 50             | 33                |          |      | 7 weeks later. Operation with normal findings. Biopsy of liver.      |
|                                  | 6        | +                 | 0                 | 3+                      | 20               | 70             | 43                |          |      | 6 weeks after onset. Operation with normal findings.                 |
|                                  | 7        | +                 | 0                 | +                       | 11.5             | 47             | 26                | 28       | 54   | 3 mon. after onset.                                                  |
|                                  | 8        | +                 | 0                 | +                       | 40               | 64             | 34                |          |      | 6 weeks after onset. Operation with normal findings.                 |
|                                  | 9        | +                 | 0                 | +                       | 133              | 71             | 65                |          |      | No extrahepatic obstruction at operation.                            |
|                                  | 10a      | +                 | 0                 | +                       | 86               | 86             | 56                |          |      |                                                                      |
|                                  | 10b      | 0                 | 0                 |                         | 55               | 30             |                   |          |      | 8 mon. later. Second slight attack.                                  |
|                                  | 11       | 0                 | 0                 | +                       | 20               | 56             | 28                | 50       | 28   |                                                                      |
|                                  | 12       | +                 | 0                 | 3+                      | 120              |                |                   | 51       | 30   |                                                                      |
| b. <i>Arsphenamine Hepatitis</i> | 13       | 2+                | 0                 | 2+                      | 75               | 71             | 56                |          |      |                                                                      |
|                                  | 14a      | +                 | +                 | +                       | 150              | 82             | 78                |          |      | 8 days after onset.                                                  |
|                                  | 14b      | 0                 | 0                 | +                       | 70               | 55             | 33                |          |      | 16 days after onset.                                                 |
|                                  | 15a      | +                 | +                 |                         | 64               | 95             | 90                | 67       | 23   |                                                                      |
|                                  | 15b      |                   |                   |                         | 50               | 82             | 60                | 62       | 19   | 4 mon. later.                                                        |
|                                  | 16       | 2+                | 0                 | +                       | 170              |                |                   | 35       | 39   |                                                                      |
|                                  | 17a      | 0                 | 0                 | +                       |                  | 75             | 40                | 71       | +1   | Clinically a slight case.                                            |
|                                  | 17b      | 0                 | 0                 | 0                       |                  | 55             | 32                |          |      | 11 mon. later.                                                       |
|                                  | 18a      | +                 | 0                 | +                       |                  | 72             | 43                |          |      |                                                                      |
|                                  | 18b      |                   |                   |                         |                  | 43             | 23                |          |      | 18 mon. later.                                                       |
|                                  | 19a      | +                 | 0                 | 2+                      | 100              | 70             | 56                | 44       | 35   |                                                                      |
|                                  | 19b      |                   |                   |                         | 22               | 50             | 30                |          |      | 2 mon. later.                                                        |
|                                  | 19c      |                   |                   |                         |                  | 58             | 37                |          |      | 9 mon. later.                                                        |
|                                  | 19d      |                   |                   |                         |                  | 48             | 26                |          |      | 16 mon. later.                                                       |
| c. <i>Toxic Hepatitis</i>        | 20       | +                 | 0                 | 0                       | 36               | —              | 50                |          |      |                                                                      |
|                                  | 21a      | 0                 | 0                 | 0                       | 7.8              | 70             | 45                | 51       | 32   | 3 mon. after onset of jaundice.                                      |
|                                  | 21b      |                   |                   |                         |                  | 64             | 34                |          |      | 5 mon. later.                                                        |
|                                  | 21c      |                   |                   |                         |                  | 55             | 36                |          |      | 7 mon. later.                                                        |
|                                  | 21d      |                   |                   |                         |                  | 64             | 42                |          |      | 10 mon. later.                                                       |
|                                  | 21e      |                   |                   |                         |                  | 38             | 18                |          |      | 13 mon. later.                                                       |
|                                  | 21f      |                   |                   |                         |                  | 74             | 50                |          |      | 15 mon. later.                                                       |
|                                  | 22a      | 2+                | 0                 | 2+                      | 10               | 52             | 25                | 37       | 72   | Poisoning with inorganic arsenic. Galactose test: 3.8 gms. in urine. |
|                                  | 22b      | 2+                | 0                 | 2+                      |                  | 48             | 25                | 32       | 49   | 3 weeks later.                                                       |
|                                  | 22c      | +                 | 0                 | +                       | 9                | 68             | 42                | 50       | 35   | 6 mon. later.                                                        |
|                                  | 23       | 2+                | 0                 | 3+                      | 202              | 84             | 80                |          |      | Fatal atophan poisoning.                                             |
|                                  | 24       | +                 | 0                 |                         |                  | 93             | 77                | 63       | 34   | Toxemia of pregnancy; patient well 3 mon. later.                     |

\* + = pathological.

TABLE III  
Chronic Hepatitis

|                                 | Case No. | Hepato-<br>megaly | Spleno-<br>megaly | Ascites | Collat.<br>Circ. | Icterus<br>Index | Rose<br>8 min. | Bengal<br>16 min. | M. G. T. |      | Remarks                                                     |
|---------------------------------|----------|-------------------|-------------------|---------|------------------|------------------|----------------|-------------------|----------|------|-------------------------------------------------------------|
|                                 |          |                   |                   |         |                  |                  |                |                   | Low      | Dif. |                                                             |
| a. <i>Atrophic Cirrhosis</i>    | 25       | 0                 | 0                 | 0       | 0                |                  | 55             | 45                |          |      |                                                             |
|                                 | 26       | 0                 | 0                 | +       | 0                |                  | —              | 95                |          |      |                                                             |
|                                 | 27       | +                 | 0                 | 0       | 0                |                  | 97             | 65                |          |      |                                                             |
|                                 | 28       | +                 | 0                 | +       | +                |                  | 91             | 81                |          |      |                                                             |
|                                 | 29       | +                 | +                 | +       | +                |                  | 79             | 68                | 88       | 5    |                                                             |
|                                 | 30       | +                 | 0                 | +       | 0                | 25               | 98             | 93                |          |      |                                                             |
|                                 | 31       | 2+                | 0                 | 2+      | 0                | 22               | 95             | 79                | 68       | 0    |                                                             |
|                                 | 32       | +                 | +                 | +       | 0                | 30               | 95             | 88                | 73       | 17   |                                                             |
|                                 | 33       | 2+                | 0                 | 0       | 0                |                  | 95             | —                 | 43       | 46   |                                                             |
|                                 | 34       | 0                 | 0                 | 2+      | 0                |                  | 95             | 55                |          |      |                                                             |
|                                 | 35       | +                 | +                 | +       | 0                | 7                | 73             | 62                |          |      |                                                             |
|                                 | 36       | 2+                | 0                 | 2+      | 0                |                  | 82             | 58                | 36       | 44   |                                                             |
|                                 | 37       | +                 | 0                 | +       | 0                |                  | 80             | 63                |          |      |                                                             |
|                                 | 38       | +                 | +                 | 2+      | +                | 6.5              | 75             | 50                |          |      |                                                             |
|                                 | 39a      | 2+                | +                 | 2+      | +                | 39               | 85             | 71                | 50       | 59   |                                                             |
|                                 | 39b      | 2+                | +                 | 2+      | 0                | 78               | 87             | 75                | 51       | 67   | 5 weeks later.                                              |
|                                 | 40       | 2+                | +                 | 0       | 0                | 25               | 90             | 75                |          |      |                                                             |
|                                 | 41       | +                 | +                 | +       | +                | 15               | 74             | 66                | 120      | 1    |                                                             |
|                                 | 42a      | 2+                | 0                 | +       | +                | 20               | 88             | 80                |          |      |                                                             |
|                                 | 42b      | +                 | 0                 | +       | 2+               |                  | 88             | 86                |          |      | 1 mon. later.                                               |
|                                 | 42c      | +                 | 0                 | +       | 2+               | 12               | 82             | 70                |          |      | 11 mon. later.                                              |
|                                 | 43       | 2+                | 0                 | +       | 2+               | 30               | 82             | 75                |          |      |                                                             |
|                                 | 44a      | 2+                | 0                 | 0       | +                | 6.6              | 60             | 25                |          |      |                                                             |
|                                 | 44b      | 2+                | 0                 | 0       | +                |                  | 43             | 20                | 42       | 73   | 3 mon. later.                                               |
|                                 | 45       | 0                 | 0                 | +       |                  | 15               | 75             | 55                |          |      |                                                             |
|                                 | 46       | 2+                | 0                 | 0       | 2+               | 15               | 65             | 40                | 86       | 40   |                                                             |
|                                 | 47       | 2+                | 0                 | 0       | +                | 10               | 70             | 45                |          |      |                                                             |
|                                 | 48a      | 2+                | +                 | +       | +                | 10               | 72             | 54                |          |      |                                                             |
|                                 | 48b      |                   |                   |         |                  |                  | 80             | 62                |          |      | 3 weeks later.                                              |
|                                 | 48c      |                   |                   |         |                  |                  | 92             | 64                |          |      | 6 mon. later                                                |
|                                 | 49       | 2+                | +                 | 2+      | +                | 6                | 69             | 40                | 38       | 61   |                                                             |
|                                 | 50       | +                 | +                 | 2+      | 0                | 7.5              | 63             | 55                |          |      |                                                             |
|                                 | 51       | 2+                | 0                 | +       | +                | 37               | 98             | —                 | 26       | 49   |                                                             |
|                                 | 52       | 0                 | +                 | 2+      | +                |                  | 80             | 70                |          |      |                                                             |
|                                 | 53       | 2+                | 0                 | 0       | 0                |                  | 70             | 50                |          |      |                                                             |
|                                 | 54       | 2+                | +                 | 0       | 0                | 11               | 62             | 48                |          |      |                                                             |
|                                 | 55       | +                 | +                 | 0       | 0                |                  | 66             | 38                |          |      |                                                             |
|                                 | 56       | 2+                | 0                 | 0       | 0                | 10               | 70             | 52                |          |      |                                                             |
|                                 | 57       | +                 | 0                 | 0       | 0                |                  | 82             | 58                |          |      |                                                             |
| b. <i>Biliary Cirrhosis</i>     | 58a      | +                 | 0                 | +       | 0                |                  | 56             | 40                |          |      | 3 yrs. later; patient died.                                 |
|                                 | 58b      | +                 | 0                 | +       | 0                | 25               | 70             | 55                |          |      | Patient died.                                               |
|                                 | 59       | 2+                | 0                 | 0       | +                | 38               | 80             | 60                | 40       | 49   | Biopsy of liver.                                            |
|                                 | 60       | +                 | 0                 | 0       | 0                | 52               | 63             | 50                | 65       | 72   |                                                             |
|                                 | 61       | +                 | 0                 | 0       | 0                |                  | 85             | 60                |          |      |                                                             |
|                                 | 62       | 2+                | +                 | +       | +                | 7.4              | 65             | 50                | 27       | 44   | Patient died.                                               |
|                                 | 63       | 2+                | 0                 | +       | —                | 172              |                |                   | 57       | 36   | Patient died.                                               |
|                                 | 64       | +                 | 0                 | 0       | 0                |                  | 70             | 50                |          |      | Patient died.                                               |
|                                 | 65       | +                 | +                 | +       | +                | 60               | 82             | 79                |          |      | Patient died.                                               |
|                                 | 66       | 2+                | +                 | +       | 0                | 41               | 74             | 48                | 40       | 51   | Patient died.                                               |
| c. <i>Banti's Syndrome</i>      | 67       | 2+                | +                 | 0       | 0                | 60               | 72             | 57                |          |      |                                                             |
|                                 | 68       | 0                 | +                 | 0       | 0                | 6                | 62             | 36                |          |      |                                                             |
|                                 | 69       | +                 | 2+                | 2+      | 2+               | —                | 100            | 67                |          |      |                                                             |
|                                 | 70       | 2+                | 2+                | 0       | 0                | 23               | 85             | 70                | 65       | 39   |                                                             |
|                                 | 71       | 0                 | +                 | 0       | 0                |                  | 90             | 70                | 41       | 53   |                                                             |
|                                 | 72a      | 0                 | 2+                | 0       | 0                |                  | 68             | 55                |          |      |                                                             |
|                                 | 72b      | +                 | 2+                | 0       | 0                | 6.9              | 76             | 48                |          |      | 2 yrs. later; splenectomy fol-<br>lowed tests.              |
|                                 | 72c      | +                 |                   | 0       | 0                |                  | 65             | 42                |          |      | 6 weeks after splenectomy.                                  |
|                                 | 73       | 2+                |                   | 0       | 0                | 30               | 88             | 82                |          |      | 7 mon. after splenectomy.                                   |
|                                 | 74       | 0                 | 3+                | 0       | 0                | 7.5              | 67             | 51                |          |      |                                                             |
| d. <i>Hemochroma-<br/>tosis</i> | 75a      | 2+                | +                 | 0       | 0                |                  | 68             | 48                |          |      |                                                             |
|                                 | 75b      | 2+                | +                 | 0       | 0                |                  | 56             | 36                |          |      | 2 mon. later.                                               |
|                                 | 76       | 2+                | 0                 | 0       | 0                |                  | 60             | 40                | 29       | 62   |                                                             |
|                                 | 77a      | 2+                | 0                 | +       | +                |                  | 58             | 35                |          |      |                                                             |
|                                 | 77b      |                   |                   | 0       | +                |                  | 60             | 33                |          |      | 3 yrs. later.                                               |
|                                 | 78a      | 2+                | 0                 | 0       | +                | 11               | 67             | 50                |          |      |                                                             |
|                                 | 78b      |                   |                   | 0       | +                |                  |                | 40                |          |      | 5 yrs. later.                                               |
| e. <i>Toxic Cirrhosis</i>       | 79       | +                 | +                 | 0       | +                | 4.8              | 78             | 47                |          |      |                                                             |
|                                 | 80       | 2+                | 2+                | +       | +                | 12               | 71             | 43                |          |      |                                                             |
|                                 | 81a      | 0                 | +                 | +       | +                | 15               | 100            | 100               | 52       | 38   | During an attack of subacute<br>yellow atrophy.             |
|                                 | 81b      | 0                 |                   | 0       | +                |                  | 92             | 84                | 79       | 6    | 6 mon. later.                                               |
|                                 | 82       | +                 | 2+                | 0       | 0                | 20               | 70             | 64                |          |      |                                                             |
|                                 | 83       | 0                 | 0                 | 2+      | +                |                  | 95             | 83                | 83       | 17   |                                                             |
|                                 | 84       | 0                 | 0                 | 0       | 0                |                  |                |                   | 122      | 30   | Rose Bengal test not done in<br>view of high icterus index. |

fact that the modified glucose tolerance was positive in only about half of the cases where it was done. Since this test depends on the amount of functioning hepatic parenchyma, it is more reliable than the Rose Bengal test in determining the extent to which the liver is involved.

## 2. MALIGNANT LYMPHOMAS

In diseases of the malignant lymphoma type, infiltration of the liver frequently occurs. A number of patients with such diseases were tested by our liver function tests, and several were found to have impaired function (Table V).

One patient with myeloid leukemia, marked spleno-megaly, and a positive modified glucose tolerance test, had a reading of only 10 per cent of Rose Bengal at the end of 16 minutes. This is a remarkably low figure even for normal individuals, who seldom have readings of less than 20 per cent. The probable explanation is that an increase of the elements of the reticulo-endothelial system in the enlarged spleen of this patient was responsible for the removal of much Rose Bengal from the blood-stream. In this light, marked spleno-megaly may mask the inability of the liver to excrete the normal amount of dye.

TABLE IV

*Correlation Between Bilirubinemia and Dye Retention  
In Hepatic Cirrhosis*

| Number of Patients | Icterus Index | Average Rose Bengal Reading |            |
|--------------------|---------------|-----------------------------|------------|
|                    |               | 8 minutes                   | 16 minutes |
| 12                 | 5—10          | 67                          | 41         |
| 12                 | 11—20         | 74                          | 59         |
| 8                  | 21—30         | 87                          | 77         |
| 7                  | Over 30       | 82                          | 66         |

### C. EXTRAHEPATIC DISEASES

The results of liver function tests in this class of patients were variable (Table VII). The following groups merit individual discussion:

**CHRONIC CHOLECYSTITIS.** Thirty-eight per cent of patients with this disease showed abnormal dye retention, and all but one of the positive cases were complicated by cholelithiasis. It was also noted that in almost all patients with gall-stones, the icterus index was 10 units or more. In our series, the duration of cholecystitis had little effect on the degree of impairment of the excretory function.

tolerance test, and determinations of bile-pigment in the blood and urine, were normal in his patients.

Turning from clinical to pathological evidence, Kerr and Rusk (16), and more recently Weller (17) and Beaver and Pemberton (18), described hepatic lesions in thyrotoxicosis, which could well explain functional impairment of the liver.

**2. Hypothyroidism.** Several of 8 patients with hypofunction of the thyroid gland gave positive results to both tests. In addition, two of the patients with impaired hepatic function had also enlargement of the liver and icterus indices of 11 and 20.

One patient with myxedema and a basal metabolic rate of 40 per cent minus, had a retention of Rose Bengal of 62 and 44 per cent at 8 and 16 minutes. Three months later, when the basal metabolic rate had been raised by the administration of thyroid substance, to 2 per cent plus, the Rose Bengal test gave normal readings. These results are in line with observations of Rowe (19) that 22 per cent of his patients with thyroid failure had demonstrable hepatic dysfunction.

TABLE V  
*Neoplasms of the Liver*

|                         | Rose Bengal Test |      |          |                     |      |        | Modified Glucose Tolerance Test |      |      | Comparison of the Two Tests |           |           |                          |                          |
|-------------------------|------------------|------|----------|---------------------|------|--------|---------------------------------|------|------|-----------------------------|-----------|-----------|--------------------------|--------------------------|
|                         | No. of Cases     | Neg. | Positive |                     |      |        | No. of Cases                    | Neg. | Pos. | No. of Cases                | Both pos. | Both neg. | R. B. pos. M. G. T. neg. | R. B. neg. M. G. T. pos. |
|                         |                  |      | No.      | Degree of Retention |      |        |                                 |      |      |                             |           |           |                          |                          |
|                         |                  |      |          | Slight              | Mod. | Marked |                                 |      |      |                             |           |           |                          |                          |
| Neoplasms of the liver. | 83               | 7    | 26       | 8                   | 9    | 9      | 15                              | 6    | 9    | 11                          | 7         | 1         | 3                        |                          |
| Malignant lymphomas.    | 12               | 7    | 5        | 1                   | 1    | 3      | 6                               | 0    | 6    | 5                           | 4         |           |                          | 1                        |
| Total                   | 45               | 14   | 31       | 9                   | 10   | 12     | 21                              | 6    | 15   | 16                          | 11        | 1         | 3                        | 1                        |

### DISORDERS OF THE THYROID GLAND

**1. Hyperthyroidism.** About two-thirds of the patients in this group in whom one or both tests were performed exhibited functional impairment of the liver. In addition, several had an increased icterus index. We also studied another group of 16 patients with the galactose tolerance test. Thirty minutes following the ingestion of 40 gms. of galactose, 13 of these patients had blood-sugar values above 150 mg. per cent. Roe and Schwartzmann (13) feel that, after ingestion of 1 gm. of galactose per kgm. of body weight, a blood-sugar level above 150 gm. per cent constitutes definite evidence of hepatic damage. In our series, the results were made more significant by the fact that the dose of galactose was only about 0.5 gm. per kgm.

In three patients who were tested following thyroidectomy, normal dye excretion was found to be re-established.

Youmans and Warfield (14) found that one-half of the patients with thyrotoxicosis in their series of 44 cases showed impairment of hepatic function by the phenoltetrachlorphthalein test, the levulose tolerance test, the icterus index and the hemoclastic crisis. Lichtman (15) demonstrated positive cinchophen oxidation tests in 16 of 20 cases of uncomplicated thyrotoxicosis. On the other hand, the urinary galactose

**DIABETES MELLITUS.** Impaired excretion of Rose Bengal was found in some cases of this disease. One patient with marked dye retention had been in severe acidosis several times. As further evidence of hepatic insufficiency, she had, even while on a rigidly controlled regime in the hospital, frequent acetoneuria and repeated hypoglycemic reactions in the presence of glycosuria.

In this connection, it is interesting that 86 per cent of the diabetic patients of Bowen, Vaughan and Koenig (21) had abnormal retention of phenoltetrachlorphthalein dye.

**ANEMIA.** A number of patients with anemias of different types showed impairment of hepatic function. In several cases of severe anemia, repeated Rose

TABLE VI  
*Correlation Between Bilirubinemia and Dye Retention  
In Neoplasms of the Liver*

| Number of Patients | Icterus Index | Average Rose Bengal Reading |            |
|--------------------|---------------|-----------------------------|------------|
|                    |               | 8 minutes                   | 16 minutes |
| 8                  | 0—25          | 58                          | 39         |
| 4                  | 26—50         | 68                          | 43         |
| 1                  | 51—100        | 70                          | 50         |
| 4                  | Over 100      | 82                          | 70         |



TABLE VII  
*Extrahepatic Diseases*

|                          | Rose Bengal Test |      |          |                     |      |        | Modified Glucose Tolerance Test |      |      | Comparison of the Two Tests |           |           |                             |                             |  |
|--------------------------|------------------|------|----------|---------------------|------|--------|---------------------------------|------|------|-----------------------------|-----------|-----------|-----------------------------|-----------------------------|--|
|                          | No. of Cases     | Neg. | Positive |                     |      |        | No. of Cases                    | Neg. | Pos. | No. of Cases                | Both pos. | Both neg. | R. B. pos.<br>M. G. T. neg. | R. B. neg.<br>M. G. T. pos. |  |
|                          |                  |      | No.      | Degree of Retentinn |      |        |                                 |      |      |                             |           |           |                             |                             |  |
|                          |                  |      |          | Slight              | Mod. | Marked |                                 |      |      |                             |           |           |                             |                             |  |
| Chronic cholecystitis    | 21               | 13   | 8        | 3                   | 3    | 2      | 3                               |      | 3    | 0                           |           |           |                             |                             |  |
| Hyperthyroidism          | 16               | 6    | 10       | 6                   | 3    | 1      | 5                               | 3    | 2    | 4                           | 1         |           | 2                           | 1                           |  |
| Hypothyroidism           | 8                | 4    | 4        | 3                   | 1    |        | 3                               |      | 3    | 3                           | 1         |           |                             | 1                           |  |
| Diabetes mellitus        | 9                | 6    | 3        | 2                   |      | 1      |                                 |      |      |                             |           |           |                             |                             |  |
| Secondary anemia         | 6                | 3    | 3        |                     | 1    | 2      | 2                               | 1    | 1    | 2                           | 1         | 1         |                             |                             |  |
| Pernicious anemia        | 4                | 1    | 3        | 2                   | 1    |        | 1                               |      | 1    | 1                           | 1         |           |                             |                             |  |
| Polycythemia             | 3                | 1    | 2        | 2                   |      |        | 2                               |      | 2    | 2                           | 1         |           |                             | 1                           |  |
| Purpura hemorrhagica     | 3                | 0    | 3        | 2                   |      | 1      |                                 |      |      |                             |           |           |                             |                             |  |
| Hemolytic icterus        | 3                | 2    | 1        |                     | 1    |        | 2                               | 1    | 1    | 1                           |           |           | 1                           |                             |  |
| Congestive heart failure | 14               | 5    | 9        | 2                   | 1    | 6      | 3                               | 1    | 2    | 3                           | 2         | 1         |                             |                             |  |
| Syphilis                 | 20               | 4    | 16       | 10                  | 2    | 4      | 11                              | 1    | 10   | 9                           | 8         | 1         |                             |                             |  |
| Nervous diseases         | 8                | 5    | 3        | 2                   |      | 1      | 7                               |      | 7    | 5                           | 3         |           |                             | 2                           |  |
| Infections               | 5                | 1    | 4        | 1                   | 1    | 2      | 5                               |      | 5    | 3                           | 2         |           |                             | 1                           |  |
| Amebiasis                | 7                | 7    | 0        |                     |      |        | 1                               |      | 1    |                             |           |           |                             |                             |  |
| Arteriosclerosis         | 5                | 5    | 0        |                     |      |        | 1                               | 1    |      | 1                           |           | 1         |                             |                             |  |
| Chronic alcoholism       | 5                | 4    | 1        | 1                   |      |        | 3                               | 1    | 2    | 1                           |           |           |                             | 1                           |  |
| Miscellaneous group      | 19               | 15   | 4        | 2                   | 1    | 1      | 7                               | 2    | 5    | 6                           | 2         | 1         | 1                           | 2                           |  |
| Total                    | 156              | 82   | 74       | 38                  | 15   | 21     | 56                              | 11   | 44   | 41                          | 22        | 5         | 4                           | 10                          |  |

Bengal tests revealed progressive improvement of dye excretion, which paralleled the recovery of the blood.

The cause of hepatic insufficiency in anemias is probably anoxemia, as was pointed out by Rich (22) in connection with the pathogenesis of certain types of jaundice. In our group of anemias, as a whole, no correlation between the degree of anemia and the rate of elimination of Rose Bengal could be made. This is not unexpected, since in addition to anemia, anoxemia is determined by several other factors, such as the state of the circulation and the efficiency of pulmonary ventilation.

**CARDIAC FAILURE.** Over one-half of our patients with chronic passive congestion of the liver had impaired hepatic function. In several instances, the Rose Bengal excretion became normal following improvement of cardiac action. The duration of congestive failure in our patients was an important factor in determining impairment of the excretory function. This is demonstrated by the fact that the average time from the onset of the first episode of congestive cardiac failure in the group with positive Rose Bengal tests was 50 months, while in the group with a negative outcome of the test, it was only 13 months. Two patients with normal dye excretion had icterus indices of 6.5 and 7. In four patients with abnormal Rose Bengal retention, the icterus index ranged from 8 to 42. Robertson, Swalm, and Konzelman (23), Jolliffe (24), and Brooks (25) are among authors who report hepatic insufficiency in cardiac disease. In this group also, anoxemia

is the most probable explanation of functional insufficiency of the liver.

**SYPHILIS.** In most patients with this disease, but without clinical evidence of hepatic involvement both liver function tests were positive. Biskind, Epstein and Kerr (8), found that 26 out of 152 ambulatory patients had hepatic damage detected only by routine performance of the Rose Bengal test. In our series of 20 cases, the proportion of positive cases was much greater, probably because we were dealing with patients who were ill enough to be in hospital. O'Leary, Greene and Rowntree (26) published a good discussion of the significance of different liver function tests in various types of syphilis.

**NERVOUS DISEASES.** The rather frequent occurrence of positive liver function tests in disease of the nervous system is unexpected, and so far lacking an adequate explanation. Fernbach (27) pointed out that patients with such disorders are hypersensitive to insulin. This would invalidate a positive outcome of the modified glucose tolerance test. But in several of our cases, the Rose Bengal test was also positive. Furthermore, Hess and Goldstein (28), Siedhoff (29), Richet, Jacquelin and Joly (30) and Crandall (31) also found evidence of hepatic insufficiency by several function tests, in various diseases of the nervous system.

**INFECTIONS.** Several patients with a variety of acute and chronic infections not involving the liver, were found to have impaired hepatic function. This is not surprising if one considers that the liver, inci-

dent to its function of detoxication, bears the brunt of toxemias which accompany infections. A number of American and foreign authors (32-37) report similar findings in a long list of infectious diseases.

**MISCELLANEOUS GROUPS.** The modified glucose tolerance test cannot be relied upon to give information on the functional state of the liver in hyperinsulinism, or in myasthenia gravis,—in hyperinsulinism because the test depends on the maintenance of a minimum blood-sugar level which is disturbed in this condition; and in myasthenia gravis because, as previously reported (2) this disease is also accompanied by abnormalities of the metabolism of carbohydrates. The outcome of the tests in the remaining 15 cases of this group in our series is not remarkable.

It was reported previously (1 & 38) that when ascites is an outstanding physical finding, the Rose Bengal test may be very helpful in making a differential diagnosis. The test is positive in portal obstruction but usually negative in tuberculosis peritonitis. In ascites due to cardiac failure, dye retention was abnormally high in six cases out of eight.

### SUMMARY

In our patients with acute hepatitis, as a group, the Rose Bengal test was positive in 94 per cent, and the

modified glucose tolerance test in 92 per cent of cases. In chronic hepatitis, the dye excretion test was positive in 96 per cent, and the metabolic test was positive in 66 per cent of patients.

In patients with neoplasms of the liver, the Rose Bengal test was positive in 79 per cent and the modified glucose tolerance in 60 per cent of cases.

A surprisingly large proportion of patients with extrahepatic diseases showed impairment by one or both tests. This applied especially to syphilis, hyperthyroidism, congestive heart failure, cholecystitis and diseases of the hematopoietic and nervous systems.

From a comparison of the two tests in 98 patients, we see that in diseases of the liver there was agreement between them in 72 per cent of cases. In the group of patients with neoplasms of the liver, agreement between the two tests was observed in 75 per cent of cases. When both tests were used in patients with extrahepatic diseases, consistent results were obtained in 66 per cent of cases. In the last group, the least degree of correlation is to be expected because the extrahepatic factors which influence carbohydrate metabolism on one hand, and the reticulo-endothelial system on the other, are apt to be more prominent than in the two groups with anatomical involvement of the liver where the hepatic factor is dominant.

### REFERENCES

1. Epstein, N. N.; Delprat, G. D., and Kerr, W. J.: The Rose Bengal Test for Liver Function. *J. A. M. A.*, May 21, 1927, 88:1619.
2. Althausen, T. L.; Gunther, L.; Lagen, J. B., and Kerr, W. J.: Modification of the Dextrose Tolerance Test as an Index of Metabolic Activity of the Liver. *Arch. Int. Med.*, 1930, 46:482.
3. Bernheim, A. R.: The Icterus Index. *J. A. M. A.*, Jan. 26, 1924, 82:291.
4. Althausen, T. L.; Biskind, G. R., and Kerr, W. J.: The Rose Bengal Test of Hepatic Function. *J. Lab. Exp. Med.*, 1933, 18:954.
5. Folin, O., and Wu, H.: A System of Blood Analysis: Simplified and Improved Method for Determination of Sugar. *J. Biol. Chem.*, 1920, 41:367.
6. Jolliffe, N.: Liver Function in Catarrhal Jaundice. *Am. J. Med. Sci.*, 1933, 186:640.
7. Althausen, T. L., and Thoenes, E.: Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes. III Chloroform Poisoning. *Arch. Int. Med.*, 1932, 50:257.
8. Biskind, G. R.; Epstein, N. N., and Kerr, W. J.: Hepatic Complications in the Treatment of Syphilis. *Ann. Int. Med.*, 1934, 7:966.
9. Althausen, T. L.: Functional Aspects of Regenerated Hepatic Tissue. *Arch. Int. Med.*, 1931, 48:667.
10. Rao, M. V. R.: The Clinical Value of the Rose Bengal Test for the Determination of the Total Functional Capacity of the Liver. *Indian J. Med. Res.*, 1932-33, 20:1009.
11. Mallory, F. B.: Cirrhosis of the Liver: Five Different Types of Lesions From Which it May Arise. *Bull. J. Hopkins Hosp.*, 1911, 22:69.
12. Dieryck, J.: Recherches expérimentales sur les épreuves fonctionnelles du système réticulo-endothélial. *Revue Belge des Sciences Médicales*, 1929, 1:685.
13. Roe, J. H., and Schwartzman, A. S.: Galactose Tolerance as a Measure of Liver Function. *Am. J. Med. Sci.*, 1933, 186:425.
14. Youmans, J. B., and Warfield, S. M.: Liver Injury in Thyrotoxicosis as Evidenced by Decreased Functional Efficiency. *Arch. Int. Med.*, 1926, 37:1.
15. Lichtman, S. S.: Liver Function in Hyperthyroidism. *Arch. Int. Med.*, 1932, 50:721.
16. Kerr, W. J., and Rusk, G. Y.: Acute Yellow Atrophy Associated with Hyperthyroidism. *Med. Clin. North Am.*, 1922, 6:445.
17. Weller, C. V.: Hepatic Pathology in Exophthalmic Goiter. *Ann. Int. Med.*, 1933, 7:543.
18. Beaver, D. C., and Pemberton, J. de J.: The Pathologic Anatomy of the Liver in Exophthalmic Goiter. *Ann. Int. Med.*, 1933, 7:687.
19. Rowe, A. W.: Endocrine Studies: XXXV. The Association of Hepatic Dysfunction with Thyroid Failure. *Endocrinology*, 1933, 17:1.
20. Althausen, T. L., and Kerr, W. J.: Hemochromatosis. *Endocrinology*, 1927, 11:377 and 1933, 17:621.
21. Bowen, B. D.; Vaughan, S. L., and Koenig, E. C.: Relation of Liver and Gall-bladder Diseases to Diabetes. *Bull. Buffalo Gen. Hosp.*, 1928, 6:41.
22. Rich, A. R.: Pathogenesis of Forms of Jaundice. *Bull. J. Hopkins Hosp.*, 1930, 47:338.
23. Robertson, W. E.; Swalm, W. A., and Konzelmann, F. W.: Functional Capacity of the Liver. *J. A. M. A.*, 1932, 99:2071.
24. Jolliffe, N.: Liver Function in Congestive Heart Failure. *J. Clin. Invest.*, 1930, 8:419.
25. Brooks, H.: Liver Disease Caused by Heart Defects. *Med. Clin. N. Am.*, 1925, 9:311.
26. O'Leary, P. A.; Green, C. H., and Rowntree, L. G.: Diseases of the Liver. VIII. The Various Types of Syphilis of the Liver with Reference to Tests for Hepatic Function. *Arch. Int. Med.*, 1929, 44:155.
27. Fernbeck, J.: Die Insulempfindlichkeit bei Gehirnerkrankungen. *Ztschr. f. klin. Med.*, 1932, 122:595.
28. Hess, L., and Goldstein, J.: Untersuchungen der Leberfunktion im chronischen Stadium der Encephalitis epidemica. *Med. Klin.*, 1931, 27:1461.
29. Siedhoff, W.: Über Störungen der Leberfunktion bei Erkrankungen des Mittelhirns. *Ztschr. f. klin. Med.*, 1931, 118:383.
30. Riehet, C.; Jacquelin, A., and Joly, F.: Manifestations hépatiques au cours d'états encéphalo-méningés. *Bull. et. mem. Soc. des Hop. de Paris*, 1931, 47:1528.
31. Crandall, L. A.: Discussion in reference 23.
32. Vogt, H.: Über den Ablauf von Leberfunktionsstörungen bei Infektionskrankheiten. *Ztschr. f. klin. Med.*, 1932, 122:33.
33. Van Creveld, S.: Function of the Liver in Scarlet Fever. *Am. J. Dis. Child.*, 1932, 44:265.
34. Steidl, J., and Heise, F. H.: Studies of Liver Function in Advanced Pulmonary Tuberculosis. *Am. J. Med. Sci.*, 1933, 186:631.
35. Lereboullet, J.: The Liver in Chronic Infections of Children. Abstract in *J. A. M. A.*, 1923, 80:284.
36. Thiebaut, F., and Dieryck, J.: L'Hépatite graisseuse tuberculeuse décelée par la galactosurie provoquée. *Compt. rend. Soc. de Biol.*, 1931, 108:960.
37. Schleussing, H.: Nekrosen in Leber, Milz und Nebennieren bei nicht vereiterten Varizen. *Verhand. d. deut. path. Gesell.*, 1927, 22:288.
38. Kerr, W. J.; Delprat, G. D.; Epstein, N. N., and Dancievtz, M.: The Rose Bengal Test for Liver Function. *J. A. M. A.*, 1925, 85:942.

# ABSTRACTS

GEORGE E. CLOEMAN, San Francisco.

*Relapsing Fever in California. Jour. Infect. Dis. Pages 282-304, 1934, Vol. 54, No. 3.*

In two articles on the epidemiology of relapsing fever in California, the author considers the carrier condition and cross-immunity and says that there is a close relationship between certain strains of the spirochetes of relapsing fever. It appears that many workers have found the spirochetes in the brains of experimental animals long after their disappearance from the blood. However, Coleman did not find the brain infectious unless the blood was also infectious.

Bedbugs, lice, fleas, and any blood-sucking insect may convey the disease mechanically, as when biting an animal or man, but it is generally believed that transmission occurs when such insects are crushed in the clothing, or when scratching contact is made with the abraded skin. Some workers have thought that the nymphs born of ticks are the infective agents.

Some animals are naturally infected with spirochetes, among them some rodents, carnivores, and insectivores, that is, porcupines, foxes, and hedgehogs. Occasionally, too, some monkeys carry the organism. Ground squirrels seem to be immune to relapsing fever.

Strains of spirochetes of relapsing fever obtained from animals several hundred miles apart showed a close relationship. Such relationship has also been found between strains from Texas and California.

J. Arnold Bargen, Rochester, Minn.

W. EVERETT GLAS, M.D., AND WILLIAM FREEMAN, M.D.

*Spontaneous Rupture of the Esophagus in Syphilis: From Worcester State Hospital, Worcester, Mass. Amer. Jour. Med. Sci., January, 1935, p. 80.*

Mosher is cited as showing the esophagus is vulnerable to every type of lesion as in 100 consecutive organs obtained in routine autopsies he found pathological lesions in 14 specimens. Spontaneous, non-traumatic, complete rupture of the esophagus is rare. There were found no reported cases of rupture of the esophagus due to luetic peri-arteritis of the wall. In 436 consecutive autopsies in their institution 44 were on patients with syphilitic involvement of the central nervous system. Five died during "paretic seizures" and of these 2 died of hemorrhage resulting from complete non-traumatic rupture of the esophageal wall. These cases are reported. It was demonstrated that syphilis caused periarteritis in the esophagus and it is assumed that the lesions weakened the wall. Attacks of retching present in paretic seizures cause extreme intra-abdominal pressure transmitted through the diaphragm to the esophageal wall. The regurgitation of autolytic gastric contents over the lining of the diseased esophagus had an erosive effect exposing the muscular layers. The epithelial lining around the rent in both specimens was almost completely denuded. In summary the authors demonstrated that syphilitic periarteritis of the esophageal wall usually leads to vascular occlusions, scar formation and damage to the epithelial lining at those points and from the foregoing combination of events; the retching and vomiting of so-called "paretic seizures" may terminate in rupture of the esophagus.

One of their patients was a 15-year-old congenital luetic with the juvenile form of general paresis, while the other was a 58-year-old patient with acquired lues and C.N.S. involvement.

Allen A. Jones, Buffalo, N. Y.

JORDAN, SARAH M., AND KIEFER, EVERETT D.

*Complications of Peptic Ulcer: Their Prognostic Significance. Journal of the A. M. A., 103:2904, Dec. 29, 1934.*

The authors studied a group of peptic ulcer patients in whom the complications of obstruction, hemorrhage and alkalosis occurred, in order to determine what effect these complications had upon the prognosis and treatment.

There were seventy-nine cases of duodenal ulcer with obstruction. Eleven per cent of this group required surgical relief of the obstruction immediately. In the remaining cases of this group, relief was obtained by medical management. The degree of obstruction was of no significance as far as treatment was concerned since equal relief was obtained by medical management in patients with over fifty per cent retention as in those with ten per cent or under. Recurrences occurred in thirty-four per cent of the obstructed cases relieved by medical treatment. Nine per cent of this group had obstructive symptoms with the recurrence.

In forty-two patients who had gross hemorrhage, forty-three per cent had recurrent attacks in the next five years. The history of two or more gross hemorrhages is decidedly more serious. In a group of nineteen such cases, only twenty-one per cent had no recurrences in five years.

There appears to be a marked correlation between ulcer activity and intolerance to alkalis: in a group of twenty patients who showed such intolerance, recurrences occurred in seventy per cent of the cases in two years.

Single hemorrhage had the least effect on prognosis, obstruction a less favorable and multiple hemorrhage and intolerance to alkalis the most unfavorable outlook.

Francis D. Murphy, M.D., Milwaukee.

WRIGHT, D. C.

*Macrocytic Anemia and Hepatic Cirrhosis. Am. J. Med. Sci., 189:115, 1935.*

Recent literature stressing the occurrence of a pernicious-anemia like blood picture in hepatic disease is reviewed.

A summary of the blood picture in 12 cases of portal cirrhosis is presented. In these the color index ranged from 0.81 to 1.36, being greater than 1 in 9 cases.

All but one of those with red cell counts below 5,000,000 had a color index greater than unity. The average mean corpuscular volume for the entire group was 90.1, being above 90 in 7 cases. Many of these patients had a leukopenia and it is noted that this change is not limited to Banti's disease with secondary cirrhosis. Six of eight patients who were subjected to gastric analysis had no free hydrochloric acid.

In addition to this group the author presents data from 41 previously studied cases. Fourteen of this latter series had a color index of one or more and free hydrochloric acid was absent in eight of eighteen patients.

The author suggests the use of the term "pernicious anemia" to describe this type of blood picture and feels that its presence should suggest the presence of hepatic disease. It has been reported in a wide variety of liver disturbances and so is not specific of any one condition. Wright feels that the most logical explanation for this type of anemia is that portal obstruction and gastric congestion adversely effect the formation of Castle's intrinsic factor.

H. Tumen, M. D., Philadelphia, Pa.

## SECTION II—*Experimental Physiology*

### Decompression of the Obstructed Biliary System of the Cat\*

#### 1. Morphological Changes

By

HAROLD L. STEWART, M.D.

and

ABRAHAM CANTAROW, M.D.  
PHILADELPHIA, PENNSYLVANIA

IN view of the fact that ligation of the common bile duct has been performed in experimental animals, for various purposes, for almost 250 years, the practically complete absence of observations relative to the morphological changes which occur in the liver following restoration of bile flow becomes difficult to understand. This apparent neglect of an important phase of the process of biliary stasis is the more striking because of the relatively frequent references to serious clinical phenomena following surgical relief of common-duct obstruction. The observations of Bell (1) upon hepatic regeneration following cholecystogastrotomy in dogs with previous common-duct obstruction and those of Stewart and Lieber (2) upon the lives of human subjects following restoration of bile flow in cases of carcinoma of the pancreas, apparently represent the only previous serious attempts to investigate this problem. The literature contains occasional sporadic references to the occurrence of spontaneous reconstruction of the common duct in animals with experimentally produced biliary stasis and to the development of spontaneous bile fistulae in such animals. However, a careful search fails to reveal any data, other than those above referred to which, as a result of carefully controlled experiments, indicate the manner in which the biliary tract reacts to the sudden restoration of bile flow following total stasis of varying duration.

In previous reports, we (3, 4) have described the morphological changes in the liver and bile ducts and certain associated functional changes which occur during total bile stasis in cats. The present experiment was designed to study the manner in which these phenomena react to biliary decompression at different stages of bile stasis.

#### METHODS OF EXPERIMENTATION

The materials and methods employed were identical with those previously described in connection with the investigation of the results of common-duct ligation in cats (4), with a single exception. In order to facilitate subsequent removal of the ligature, the duct was ligated close to the duodenum, with sterile linen tape, 3 mm. wide, tied in a

double surgical knot. Autopsy upon animals that died during the period of total stasis revealed the fact that in two cases in which this knot appeared to be loose, bile could be forced from the bile ducts into the duodenum, whereas in several in which it appeared to be tight, bile could not be forced past the point of obstruction. Consequently, the data reported here are only those obtained in animals in which the ligature was firmly in place at the time of operation for its removal. This was performed in different animals at varying intervals following ligation of the common duct. At the time of the secondary operation, sections of liver and kidney were removed in most instances for the purpose of comparing the lesions of stasis with those of decompression in individual cases. The ligature was removed by carefully releasing the knot by means of two pairs of mosquito forceps and only those animals are included in this report in which the contents of the ducts promptly filled the segment distal to the point of ligation. The animals were subsequently killed and autopsied at varying intervals following release of obstruction. All instances were excluded in which the duct system was not perfectly patent and in which bile could not be readily expressed through the ampulla of Vater. By the observance of these precautions we feel reasonably certain, although we cannot be absolutely sure, that the duration of total stasis and that of decompression have been accurately timed.

At the time of operation in many cases, the wall of the common duct was found to be necrotic and eroded at the site of the ligature; in several the duct was ruptured in attempting to remove the ligature; in a few instances spontaneous rupture of the duct had occurred above the point of ligation. These animals were excluded from the present report as were those in which any evidence of infection was noted other than small, localized stitch infections. The following data therefore represent observations upon 19 cats with total bile stasis of 1 to 16 days duration followed by decompression of 1 hour to 7 days duration. In 12 instances cholecystectomy was performed at the time of ligation of the common duct.

#### EXPERIMENTAL OBSERVATIONS

##### GROSS CHANGES

Following removal of the obstructing ligature, the liver diminished in size and became rather flabby with wrinkling of the capsule. The consistency varied, de-

\*From the Pathological Laboratories of the Jefferson Medical College and Hospital, the Jefferson Hospital Tumor Clinic and the Laboratory of Biochemistry, Jefferson Hospital.  
Submitted January 16, 1935.

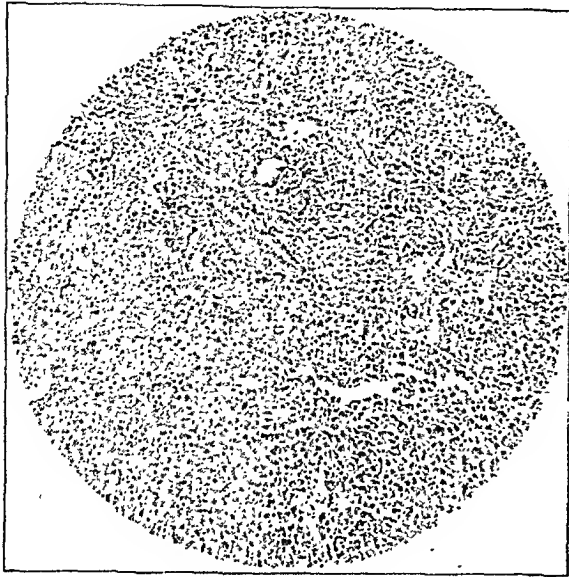


Fig. 1.

pending upon the duration of stasis, the degree of fibrosis and the extent of regressive changes. In cases in which complete stasis had existed for 1-8 days, the previously distended extrahepatic ducts collapsed promptly as illustrated by their condition in Cat 119, 2 hours following relief of stasis of 6 days' duration. The increased fibrosis associated with more prolonged stasis (10-15 days) appeared to interfere with complete collapse of the extrahepatic ducts, which were observed to be markedly dilated even after 4 days of decompression.

Bile was present in the intestine and could be expressed through the ampulla of Vater in all but 2 cases (Cats 63 and 86), in which there was apparently acute suppression of bile formation. In the former, the extrahepatic ducts contained a thick white, mucoid material and the intrahepatic ducts were empty; in the latter the ducts contained a small quantity of thin pale fluid. No constant alteration was noted in the color or consistency of the bile in the other animals.

#### PIGMENTATION

Pigmentation of the liver during total bile stasis in cats is extremely variable in distribution and intensity, bearing no constant relation either to the duration of stasis or to the degree of bilirubinemia (3, 4). A similar variability was observed following decompression although, in general, the degree of pigmentation tended to diminish rather rapidly following restoration of bile flow. However, a few distinct exceptions to this general rule were noted. In cat 86, in which there appeared to be practically complete suppression of bile secretion, pigmentation was more marked one day after decompression than after 7 days of stasis. An increase was also present in Cat 87, 7 days after decompression of an obstruction of 4 days' duration. Similar changes were noted in cats 119, 152 and 82. In some instances, the pigment granules appeared to stand out more distinctly than in the static liver cells.

In a few cases, particularly Cat 119, a change appeared to occur in the relative distribution of pigment in the hepatic and Kupffer cells. Only 2 hours after release of obstruction, the Kupffer cells, which had previously contained large quantities of pigment, had

Fig. 1. Sporadic necrosis and intralobular architectural distortion, with loosening of the hepatic cells from their reticular attachments following decompression. Photomicro. mag. circ. 80 x.

become markedly swollen and vacuolated and distinctly less pigmented. This decrease in pigmentation appeared to be coincidental with the increase in vacuolization and the vacuoles appeared to occupy areas previously occupied by pigment granules. A simultaneous increase in pigment was noted in the hepatic cells and canaliculi.

In two instances (Cats 131, 128) in which the subcapsular zone showed marked regressive changes, but not hyaline necrosis, this area was much more deeply pigmented than is ordinarily the case in the liver of stasis. In Cat 132, in which pigmentation was generally marked, scattered throughout the liver were large cells, apparently hepatic cells, which were vacuolated and deeply pigmented. In many places they were collected in groups, the largest comprising about 35 cells, the line of demarcation from the surrounding parenchyma being usually sharp and consisting of a canaliculus. These lesions which occurred indiscriminately in all parts of the lobule were regarded as probably localized areas of necrosis, the pigment granules standing out against the necrotic and vacuolated cytoplasmic background. Sections of this liver, stained with Nile blue sulphate, contained a large amount of lipid material, confined almost exclusively to Kupffer cells except for the above-mentioned necrotic areas which were also heavily laden with lipid droplets, standing out in sharp contrast to the surrounding fat-free parenchyma.

In one animal (Cat 152) small nodular, pigmented lesions, situated at the periphery of several of the lobules, were observed in various stages of regression (Fig. 2). The degree of pigmentation of the mononuclear cells of this lesion diminished progressively and there was a simultaneous increase in the degree of vacuolization of these cells. Coincident with these changes, there was a progressive increase in lymphocytic and chiefly plasma cell infiltration.

#### ARCHITECTURAL CHANGES IN PARENCHYMA

Disruption of the intralobular architectural pattern constituted one of the most prominent features of the decompressed liver. In its advanced form it presents a rather characteristic picture (Fig. 1). The cells lie singly or in short cords of 6-15 cells, in varying stages of degeneration, necrosis and cytoplasmic disintegration, with fraying and tearing of the reticulum. As a result of these changes the canaliculi frequently communicate directly with the perivascular tissue spaces which are usually edematous and may contain red blood cells, extruded from ruptured sinusoids. The architectural distortion is usually most marked in the inner third of the lobules and about the larger bile ducts but, in some cases, may be confined to the subcapsular region or may occur in localized areas throughout the parenchyma.

This condition of parenchymal disorganization was present in some degree in every case, following decompression of 1½ hours' to 7 days' duration. The changes were minimal in animals in which biliary stasis had existed for only 24 hours, increased more or less progressively to reach a maximum following 6-10 days of stasis, and were less marked and ex-

Fig. 2. Nodular pigmented lesion situated peripherally in a lobule. Note vacuolization in pigmented cells in the portion of the lesion to the right; the remainder of the lesion is infiltrated with plasma cells and lymphocytes. Photomicro. mag. circ. 400 x.

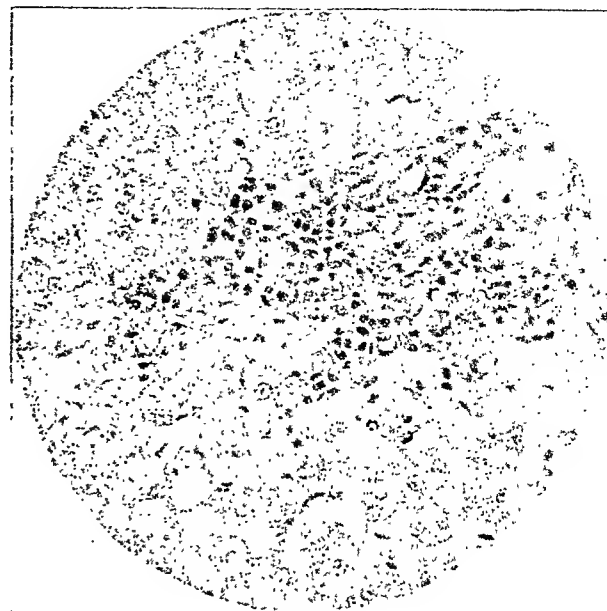


Fig. 2.

tremely inconstant in cases following obstruction of 11-15 days' duration. In the latter, the architectural distortion was generally confined to or most marked in the region of the larger bile ducts.

#### REGRESSIVE CHANGES

Although somewhat variable, the degree of sporadic necrosis tended to be more marked following decompression than during stasis. This was particularly true in cases with decompression of relatively brief duration and, to a lesser degree, in those in which the pre-existing period of obstruction had been limited to 1-3 days. The extent of sporadic necrosis in some instances is illustrated by cases 131, 119 and 120, in which only 20-50 per cent of the hepatic cell nuclei could be identified in stained sections. This lesion appeared to be less marked following decompression of longer duration (viz. Cat 82), due probably to restoration of the parenchyma by active regeneration of hepatic cells.

Focal mid-zonal areas of necrosis were noted in 5 animals, 119, 82, 64, 72 and 116, with stasis of 6, 8, 11, 11 and 12 days' duration, and decompression of 2 hours, 3 days, 1 day, 4 days and 1 day respectively. In each instance these lesions were in an advanced state of regeneration. In Cat 116 these lesions showed a marked plasma cell infiltration and in the others they were almost completely effaced by regenerating hepatic cells. In Cat 82 the cells at the periphery of the area of necrosis were sending short cord-like processes into the lesion, which showed mitotic figures and other evidences of regeneration.

In the liver of stasis, the tissue immediately beneath the capsule consists of pale-staining, swollen, vacuolated or finely-reticulated hepatic cells with sharply outlined borders and indistinct oval nuclei which frequently appear as basophilic smudges; these degenerative changes tend to remain stationary unless complete necrosis supervenes (3). No change was noted following decompression in some cases. In others, as in Cats 86, 121 and 82, the hepatic cells in the subcapsular zone showed distinct improvement (1-3 days decompression). The chromatin material in the nucleus stained more sharply, the cells decreased in size and both nucleus and cytoplasm assumed a more normal appearance. Many of the cells were smaller than previously and the cytoplasm became smoother, less reticulated and more deeply staining. These changes were accompanied by a coincident dilation of the sinusoids in this area. In Cats 72 (stasis 11 days, decompression 4 days), and 64 (stasis 11 days, decompression 1 day) the subcapsular zone was still finely reticulated and many cells were necrotic but individual cells here and there had assumed a normal appearance. In Cat 128 (stasis 15 days, decompression 2 days) this area was badly damaged although the regressive changes in the remainder of the parenchyma were minimal. Cats 143, 147 and 63 showed a distinct increase in the extent and degree of degeneration, necrosis and vacuolization following decompression of 1-3 days' duration. An area of subcapsular hyaline necrosis was present in Cat 116 following decompression of 24 hours duration; although this lesion

was not observed in the biopsy specimen (12 days stasis) it cannot be regarded as necessarily absent at that time because of the possible variable distribution of such lesions in the liver of total stasis.

A variable degree of hyaline necrosis was present at autopsy about the larger bile ducts in 5 cases (Cats 119, 121, 77, 72 and 116) but in no instance was it possible to determine whether this lesion had increased in extent or degree following decompression because of the impossibility of obtaining biopsy specimens from these areas of the liver during stasis.

#### BILIARY PASSAGES AND CONNECTIVE TISSUE

A conspicuous point of difference between the liver of stasis and that of decompression lay in certain prominent changes in the epithelial cells of the small proliferated and medium-sized bile ducts and in the infiltrating lymphocytes, monocytes, plasma cells and polymorphonuclear leukocytes. In several instances the cytoplasm of these cells was completely vacuolated, the portal radicles in paraffin sections bearing a close resemblance to xanthomatous nodules (Fig. 3). The nature of the substance responsible for this appearance was not determined but it did not stain with fat or glycogen stains. The monocytes and polymorphonuclear leukocytes appeared to be involved in the process of vacuolization earlier and more extensively than the plasma cells and lymphocytes, which seemed to resist this change. In some instances the resulting enlargement of the epithelial cells and infiltrating cells was so marked as to produce complete occlusion of the lumens of the smaller and medium-sized ducts. The epithelial lining cells of the larger ducts exhibited this change to a less extent and, in Cat 86, a similar process was observed in the cells of a localized inflammatory reaction on the peritoneal surface of the liver. In other cases the vacuolated epithelial cells were observed in process of phagocytosis by the invading macrophages, which were occasionally accumulated in masses within the lumens of the ducts.

In the early phase of this process the bile duct epithelial cells appeared pale and swollen and stained irregularly; the nuclei were large and clear and the chromatin material appeared to be diminished. Some



Fig. 3. Portal area showing extensive swelling and vacuolization of the lining epithelial cells of a medium-sized bile duct which are infiltrated with inflammatory cells; "a" indicates lumen, "b" basement membrane. The process involves many of the infiltrating cells and is also present, although less marked, in the larger duct (c) in the lower portion of the field. Note distortion of structural arrangement on the left. Photomicro. mag. 200 x.

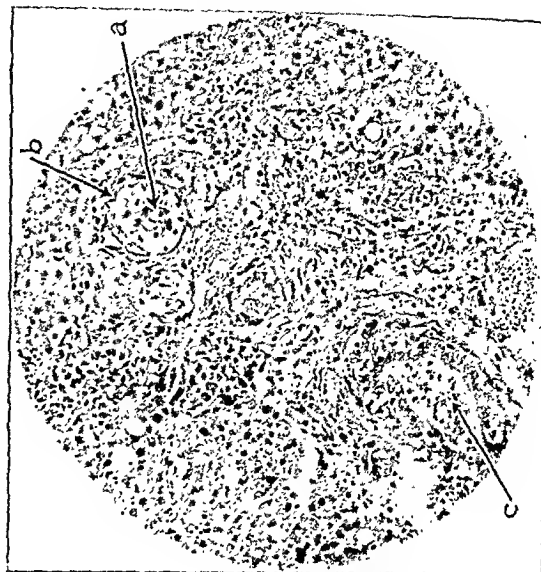


Fig. 3.

of these cells were undergoing necrosis and cytoplasmic disintegration but these changes were relatively inconstant and inconspicuous. The development of this phenomenon seemed to be related more directly to the duration of stasis than to that of decompression, for it was not observed in any case in which common duct obstruction had been maintained for less than 4 days. It was noted in variable degree of intensity as early as 1-3 hours following decompression in animals with 6-8 days stasis (Cats 119, 120), and was most marked in Cat 86 (stasis 7 days, decompression 1 day). In Cat 87 (stasis 4 days, decompression 7 days) vacuolization was still present in the smaller but very slight in the medium-sized ducts and appeared to persist longest in the basal portion of the cells.

During stasis the mucosa of the larger ducts undergoes progressive proliferation which becomes very marked, particularly after the tenth day when it presents a papillary and adenomatous appearance, with multiplying cylindrical epithelial cells several layers deep supported by hyperemic fibrous tissue with a few inflammatory cells. The smaller ducts show mitotic figures and budding within the first 24 hours and grow out from the portal radicles in the form of cords of cells supported by connective tissue with no demonstrable lumen. They insinuate themselves between the hepatic cells of adjacent lobules, the majority of which, after the 21st day, are surrounded by a collar of these proliferating elements. As early as 1½ hours after release of obstruction in an animal (Cat 123) with 10 days stasis, the adenomatous formations in the mucosa of the larger ducts showed marked epithelial cell necrosis, the disintegrating cytoplasm being continuous with the granular albuminous contents of the lumen. Some of the bile-duct cells were being phagocytosed by macrophages and polymorphonuclear leukocytes and the epithelial lining showed marked denudation, the cells being cast off into the lumen. This regressive process became progressively more marked with prolongation of the state of decompression (Cat 72, stasis 11 days, decompression 4 days). The connective tissue about the larger ducts became markedly edematous and more fibrillar and less compact than during complete stasis. The newly proliferated smaller ducts also underwent regression and, with the accompanying connective tissue, were displaced and crowded by regenerating hepatic cells, became atrophied and eventually disappeared (Figs. 4 and 5). Isolated cords of bile duct cells could be seen lying in small groups, without a lumen, and long cords were frequently interrupted by actively regenerating hepatic cells. These changes were marked within the first 3 days following relief of stasis. In some cases, lumenization of certain cords occurred coincidentally with compression, atrophy and disappearance of others and eventually, as in Cat 87 (stasis 4 days, decompression 7 days), the proliferated ducts regressed to the point where every one which remained was lumenized.

In several cases (especially Cat 86), as in stasis, destruction of newly proliferated ducts was effected by the accumulation in their lumens of a pink hyaline secretion; this produced compression and necrosis of the lining epithelial cells which appeared to liberate a stringy, basophilic substance which was ultimately removed by the action of phagocytic cells. With the restoration of bile flow, canalicular casts, which are numerous during stasis, gradually disappear and in favorable cases the canaliculi ultimately reassume their normal appearance. Recovery was practically complete in one animal 7 days after release of obstruction (Cat 87). Marked architectural distortion was naturally associated with a corresponding degree of canaliculi disruption but marked dilatation of the canaliculi persisted in some cases of protracted stasis with little or no disturbance of the architectural pattern.

#### BLOOD VESSELS AND KUPFFER CELLS

The sinusoids, which during stasis had been compressed to a variable degree by proliferating and distended bile ducts, frequently became dilated and hyperemic during decompression. This change was observed in the subcapsular area as well as in the parenchyma generally and was noted as early as 2 hours (Cat 119) after relief of obstruction of 6 days duration. This state of hyperemia and dilatation rendered the outlines of the sinusoids and the liver cell cords more distinct than during stasis. In some instances the reticular walls of the sinusoids were torn, resulting at times in small hemorrhages. The Kupffer cells were very prominent, swollen and vacuolated, and frequently were actively phagocytosing red blood cells. Their nuclei were often large and partially karyolyzed. Many Kupffer cells, swollen and filled with debris, were observed within the lumen of the central and sublobular veins and sinusoids, the latter being at times almost completely occluded by these elements. Changes in the pigmentation of the Kupffer cells have been described previously.

In several instances there was marked edema of the perisinusoidal and other perivascular tissue spaces and occasionally previously compressed arteries were assuming a more normal appearance. In one case (Cat



82) there was a large area of infarction associated with thrombosis of large branches of the hepatic artery and portal and hepatic veins. In Cat 63, thrombosis of some of the smaller portal radicles was associated with apparently acute suppression of bile secretion.

#### REGENERATION

Although regression of bile ducts is a very prominent feature of decompression, mitotic figures occasionally were observed in the bile-duct epithelium, indicating an attempt at active regeneration. Of particular interest, however, were the regenerative changes in the hepatic parenchyma, which constituted one of the outstanding features of the liver of decompression. Although present elsewhere, these changes were most pronounced in the region of the smaller portal radicles where the hepatic cells, during the period of stasis, had gradually become atrophied and compressed by the distended and proliferating bile ducts. In this situation the hepatic cells became swollen, more numerous and more prominent, with a clear, finely reticulated cytoplasm and hyperchromatic nuclei. Binucleation, multiple nuclei and active mitosis were frequently observed. These newly formed cells insinuated themselves among the proliferated ducts, compressing them and crowding them aside (Figs. 4 and 5); in some instances small islands of bile-duct cells had been apparently snared off and were surrounded by the regenerating hepatic cells. In the majority of cases the bile-duct epithelial cells and the young hepatic cells could be readily identified on the basis of the characteristic appearance of the latter, described above, and the small compressed, pyknotic, sharply staining condition of the former. In some instances, however, certain cells in this situation could not be positively identified.

During stasis, the regressive changes in the subcapsular zone either remain stationary or eventuate in a narrow band of hyaline necrosis. The necrotic material in this area is cleared away by phagocytic cells and the still viable cells in the adjoining parenchyma, without showing binucleation or mitosis to any appreciable extent, appear to move in a sheet toward the capsule, against which the phagocytes and necrotic material, which is being rapidly evacuated, are being compressed (4). In spite of careful search in more than 70 animals, mitotic figures and other evidences of regeneration were not observed in the subcapsular zone proper during stasis. Following decompression, particularly in cases with 4-10 days stasis as described previously, improvement in the condition of the cells in this area was evidenced by diminution in vacuolization and by accentuation of cellular outline and of the chromatin material in the nucleus. This improvement progressed until the majority of the cells of the subcapsular zone had reassumed an essentially normal appearance (Cat 87, stasis 4 days, decompression 7 days). In sharp contrast to the findings during stasis, numerous mitotic figures were observed in this area following decompression (Fig. 6), as were other evidences of active regeneration, such as binucleation, multiple nuclei and nuclear enlargement and hyperchromasia. Complete restoration of the subcapsular region as well as the remainder of the parenchyma appeared to be a relatively slow process, for active mitosis was noted as late as the seventh day following relief of obstruction (Cat 87).

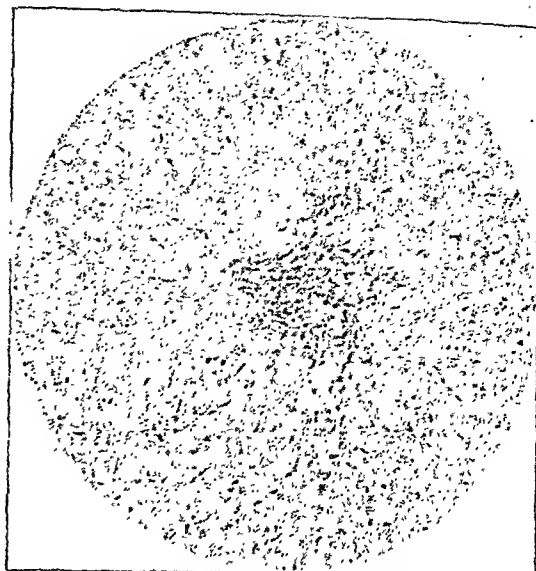
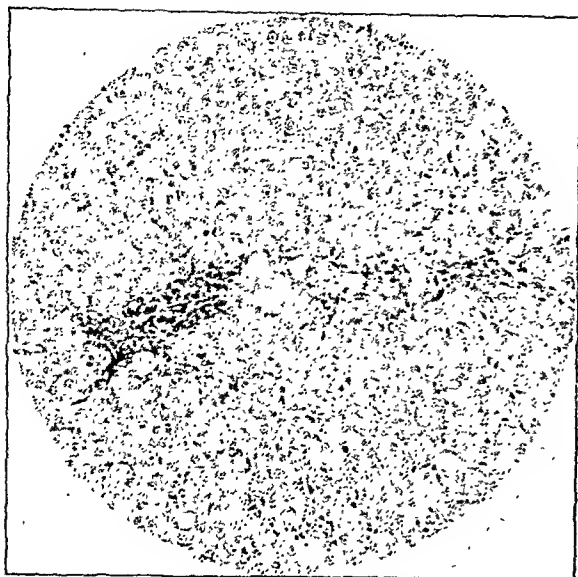
The frequency with which mitotic figures were observed in the hepatic cells was very striking, mitosis being in general much more active during decompression than during stasis; in some cases as many as 3 mitotic figures were noted per oil immersion field (Fig. 7). In animals in which stasis had been maintained for 10-15 days, decompression was accompanied by very little evidence of active regeneration despite the fact that nuclei of normal appearance were exceedingly numerous. Whatever evidence of regeneration was present was practically limited to the region of the larger bile ducts. In Cat 86, with apparently complete suppression of bile secretion, regeneration of hepatic cells was very slight, no mitotic figures were observed and the cells about the proliferating bile ducts remained compressed.

#### DISCUSSION

##### PIGMENTATION

Following surgical decompression of an obstructed biliary system in man, hepatic pigmentation diminishes progressively and rather rapidly in patients who survive the immediate effects of the operation (2). In the cat, however, the distribution and intensity of pigmentation, which are extremely variable during total stasis, are equally variable during decompression. The changes in the relative distribution of pigment in the Kupffer and hepatic cells noted in Cat 119, 2 hours after relief of obstruction, are of extreme interest. The simultaneous decrease in Kupffer cell pigmentation and increase in hepatic cell pigmentation suggest a rapid movement of bile pigment in this direction following restoration of bile flow. The increase in the degree of pigmentation of the subcapsular zone during decompression in certain cases and the apparent increase in pigment in scattered areas of necrosis in others are interesting but the significance of these changes is conjecturable.

The exact nature of the small nodular pigmented lesions noted in Cat 152 could not be determined. Their situation at the periphery of the lobule is identical with that occupied by biliary necroses in man. The component cells of these lesions could not be positively identified when observed during total stasis in a previously studied group of animals; they were regarded either as hepatic cells, bile duct epithelial cells or macrophages and were believed to have resulted possibly from interference with the passage of bilirubin from the canaliculi into the duct system due to the interposition of fibrous tissue. During decompression it became apparent, as a result of diminution in the intensity of pigmentation of these lesions, that at least some of the constituent cells are hepatic cells. This suggests that the remaining, still unidentifiable cells may also be hepatic cells, but no definite statement can be made in this connection on the basis of the available material. As the morphological characteristics of these lesions became more readily demonstrable, an alveolar arrangement was suggested, but the degree of architectural distortion, although not marked, was sufficient to preclude the possibility of more positively identifying their structural characteristics. The fact that bile ducts could never be demonstrated in these lesions, coupled with the fact that proliferated ducts in various stages of regression were extremely numerous elsewhere throughout the parenchyma, suggests two possibilities: (1) that bile ducts may actually constitute the structural basis of



Figs. 4 and 5. Illustrating different stages in regression of small proliferated bile ducts. Note encroachment by newly regenerated hepatic cells and the characteristic large, clear and pale appearance of the latter. Photomicro, mag. 200 x.

these nodules, being obscured by the relatively intense pigmentation; (2) that these pigmented lesions develop at the site of a bile duct which has undergone complete destruction as a result of changes associated with total bile stasis. The significance of the plasma cell infiltration and of the vacuolization of the constituent cells of the lesion, which progressed simultaneously with the decrease in pigmentation, cannot be stated.

#### ARCHITECTURAL CHANGES

Disruption of the intralobular architectural pattern following decompression in the cat is quite similar in appearance and distribution to that noted in human beings by Stewart and Lieber (2). The pathogenesis of this lesion, as discussed by these authors, probably is dependent purely upon mechanical factors resulting from the sudden fall in the elevated intraductal and probably intravascular pressures consequent upon release of obstruction of the common bile duct. The fact that distortion of architecture was slight in animals following stasis of only 24 hours' duration may be attributable, on this basis, to a relatively slight increase in these pressures during the early stage of stasis. The inconstancy of these changes in animals in which biliary obstruction had existed for 11-15 days may be due to the fact that the increase in fibrous tissue which develops during this period tends to prevent the marked loosening and shaking-up of hepatic cells which is a striking feature of decompression in cases with stasis of briefer duration.

#### REGRESSIVE CHANGES

The increase in the degree of sporadic necrosis noted in the majority of cases in the early stage of decompression following obstruction of relatively brief duration (1-3 days) appeared to represent merely an accentuation of those lesions already present during stasis. Although the process of restoration of the parenchyma in these areas of sporadic necrosis was not followed by serial biopsy examinations in individual cases, the fact that these lesions were less marked in animals at longer intervals after release of common-duct obstruction suggests that their disappear-

ance was due to parenchymal restoration by actively regenerating hepatic cells (*viz.* Cat. 82).

It is possible that the areas of sporadic necrosis in the cat are essentially analogous to the regressive lesions which are a prominent feature of the liver of decompression in human subjects. However, in man these lesions are most marked about the central veins, extend peripherally into the lobules and bear a close anatomical and quantitative relation to the associated distortion of intralobular architecture. In the cat, this latter relationship is not maintained and the regressive changes are distributed sporadically throughout the lobule, bearing no particular relation to the central veins or portal radicles. Moreover, this necrotic process never attained the proportions in cats which it does in man and, even when marked, was not accompanied by evidences of suppression of bile secretion.

#### BILE PASSAGES AND CONNECTIVE TISSUE

The process of vacuolization of the small and medium-sized bile ducts, which was an outstanding feature during decompression in cats, was never observed following surgical relief of bile stasis in humans. Likewise it was never present in the liver of stasis of humans or cats. Except for the fact that the substance responsible for the vacuolated appearance of these cells did not give the characteristic staining reaction of fat, lipoids or glycogen, its chemical nature was not determined. The possibility that this change may be due to edema cannot be disregarded, although this seems unlikely in view of the absence of comparable grades of edema throughout the hepatic parenchyma and the presence of similar changes in the infiltrating macrophages and, occasionally, in inflammatory cells in certain cases. Moreover, the absence of precipitated granular material within the vacuoles would indicate that if this phenomenon is due to edema, the fluid must have an unusual chemical composition in that it contains an extremely small amount of protein, if any. The fact that the cells involved frequently are phagocytosed by macrophages suggests that the process is to some extent regressive in nature; however, some of the affected cells of the bile-duct

epithelium undoubtedly recover completely and the various stages in the disappearance of the vacuoles could be followed in some instances, the process persisting longest in the basal portion of the cells.

With the removal of the apparent stimulus to proliferation coincident with the restoration of bile flow, restoration of the normal structure of the larger bile ducts was effected by necrosis, desquamation and phagocytosis of their extensively proliferated lining epithelial cells. The occasional disappearance of medium-sized ducts by the accumulation of hyaline material and phagocytic cells within their lumens was noted during decompression as during stasis. Changes in the newly-proliferated smaller bile ducts constituted a striking feature of the decompression. The majority of these underwent regression and were displaced, compressed and the continuity of their cords interrupted by actively regenerating hepatic cells so that eventually they became atrophied and disappeared. The connective tissue accompanying these

relation to groups of necrotic hepatic cells, mitotic figures, as well as other signs of active regeneration, were most numerous in the peripheral portions of the lobules in relation to the smaller portal radicles (Fig. 6). The changes which occur in the smaller bile ducts and adjacent hepatic cells during decompression are in sharp contrast to their condition during the period of obstruction. During total stasis, these ducts and their supporting stroma undergo proliferation and regeneration, whereas the dominant change in the adjacent parenchyma is regressive in nature. During decompression these conditions are reversed, the proliferated elements in the smaller portal radicles undergoing rapid involution and regression coincidently with and probably as a result of active regeneration of the surrounding hepatic cells.

Mitotic figures in bile duct epithelium can be readily distinguished from those in hepatic cells on the basis of their respective characteristics. Mitosis was occasionally noted in cells of proliferated bile ducts

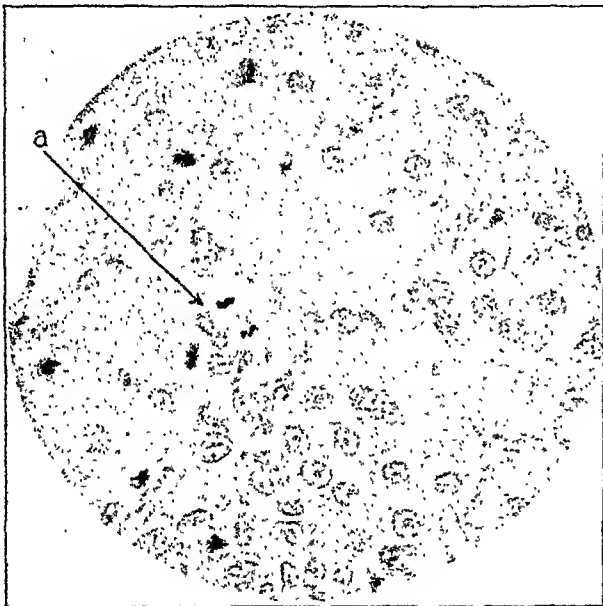


Fig. 6. Mitotic figure in hepatic cell (a) in subcapsular zone. Note group of bile duct epithelial cells immediately below and margin of liver on the left border of the illustration. Photomicro. mag. circ. 700 x.

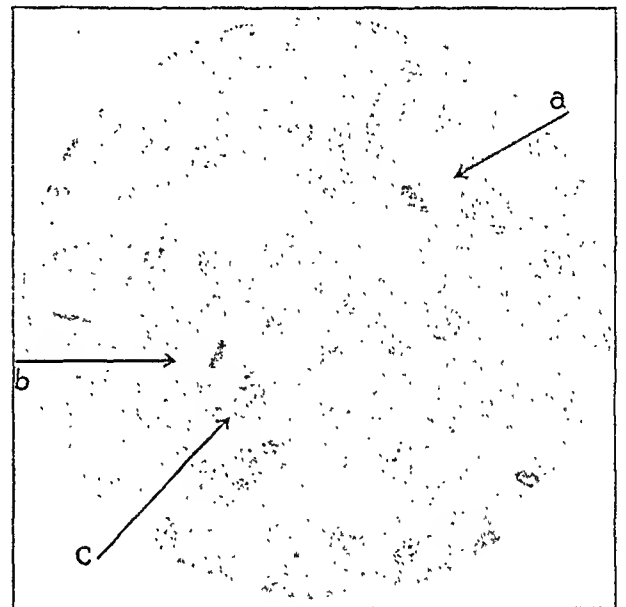


Fig. 7. Three mitotic figures in single oil-immersion field (a, b and c), in mid-zone of lobules, "c" being slightly out of focus. Photomicro. mag. circ. 800 x.

proliferated bile ducts was ultimately compressed into thin strands of compact collagen fibrils interspersed with a few pyknotic, spindle-shaped nuclei. In some cases, lumenization of certain cords occurred coincidentally with regression of others, until eventually every small bile duct which remained was lumenized.

#### REGENERATION

In the cat, as in man, there is marked evidence of active regeneration of hepatic cells following release of obstruction of the common bile duct. In the latter, however, we were unable to find mitotic figures at any time during either total stasis or decompression, whereas, in the cat, active mitosis was noted under both conditions, being more marked during decompression. There is no obvious explanation for the absence of mitotic figures in the subcapsular zone during total stasis and their appearance in this situation following restoration of bile flow. Although distributed generally throughout the hepatic parenchyma, frequently in

which were undergoing regression but in no instance was it possible to demonstrate a transition from these cells to hepatic cells. The cells in these regions, referred to above, which could not be positively identified as either bile-duct epithelial cells or hepatic cells, did not appear to represent a transition stage of this nature.

A point of particular interest is the fact that the activity of regeneration appeared to diminish after the tenth day of stasis both in animals in which obstruction was maintained for a longer period and in those in which decompression was effected after this time. In view of the activity of the regenerative process during the earlier period of stasis, it is probable that the majority of the hepatic cells which are viable at this time were generated following ligation of the common bile duct. The diminished activity of regeneration in such animals, even during decompression, may be dependent upon a diminished reactivity

to stimuli which would ordinarily produce either regressive or regenerative changes in hepatic cells with stasis of briefer duration.

### SUMMARY

1. Diminution in the intensity and distribution of pigmentation is extremely variable during decompression of the obstructed biliary system of the cat. In some cases a decrease in Kupffer cell pigmentation occurred simultaneously with an increase in hepatic cell pigmentation, suggesting a rapid movement of bile pigment in this direction. Peculiar pigmented nodular lesions were noted, the exact nature of which could not be determined.

2. Increase in the extent of regressive changes and a rather characteristic disruption of the intralobular architectural pattern were prominent features of the liver of decompression.

3. A rather constant finding was that of a peculiar process of vacuolization involving the lining epithelial cells of the smaller and medium-sized bile ducts and the associated infiltrating cells. The nature of the sub-

stance responsible for this vacuolization was not determined but it was apparently neither fat nor glycogen.

4. The proliferated bile ducts tended to regress to the point of complete disappearance. This occurred simultaneously with and was perhaps largely dependent upon active regeneration of adjacent hepatic cells which eventuated in lobular expansion and more or less complete restoration of the parenchyma in these situations. These regenerative changes, in which active mitosis played a prominent part, also occurred sporadically throughout the remainder of the lobule, frequently in relation to single and aggregated necrotic hepatic cells. In the restoration of the hepatic parenchyma, the process of active regeneration was supplemented by the recovery of degenerated but still viable cells.

### REFERENCES

1. Bell, L. P.: *California and West Med.*, 25:503, 1926.
2. Stewart, H. L., and Lieber, M. M.: *Arch. Path.*, 18:30, 1934.
3. Stewart, H. L., and Lieber, M. M.: *Arch. Path.* (in press).
4. Cantarow, A., and Stewart, H. L.: *Am. J. Path.* (in press).

## The Parallel Concentration of Enzymes in the Pancreatic Juice\*

By

STEWART G. BAXTER, M.D., Ph.D.  
MONTREAL, CANADA

IT was established some time ago by Babkin (1904) and Sawitsch (1909) that the three principal enzymes of the pancreatic juice—trypsin, lipase and amylase—are secreted by the pancreatic gland of the dog in parallel concentrations. The greater the digestive power of any one of these enzymes in the juice, the greater was that of the other two. To demonstrate these relations between the enzymes it was necessary to activate the protrypsin of the inactive pancreatic juice with the enterokinase of the intestinal juice, and the prolipase with bile. The amylase of the pancreatic juice is secreted in an active form and does not require any activator. Food containing fat stimulated a flow of pancreatic juice rich in all three enzymes, whereas carbohydrate and especially protein produced a secretion with a lower digestive power. Babkin and Tichomirow (1909) then found that the higher the proteolytic, and hence the lipolytic and amylolytic, power of canine pancreatic juice, the higher was its nitrogen concentration. In comparing the nitrogen concentrations of different samples of the juice, they found that the relations between them corresponded very closely with the relations between the squares of the millimeters of the digested protein of the corresponding juices in the Mett's tubes. Therefore, instead of estimating the enzymatic power in different samples of the pancreatic juice, they suggested that the digestive power of the juice might be more accurately determined by ascertainment of the nitrogen concentration by Kjeldahl's method.

From study of a case of pancreatic fistula in a human subject, Wohlgemuth (1907) likewise found that trypsin, lipase and amylase were secreted by the pancreatic gland in parallel concentrations. In Table I are quoted figures for the concentration of trypsin,

TABLE I

| Food         | Volume c.c. | Trypsin | Amylase | Lipase |
|--------------|-------------|---------|---------|--------|
| Carbohydrate | 75.0        | 5.3     | 4.8     | 225.0  |
| Protein      | 65.0        | 10.89   | 6.25    | 529.0  |
| Fat          | 35.0        | 14.97   | 10.89   | 954.8  |

amylase and lipase in the pancreatic juice of this patient after meals rich in carbohydrate, protein and fat. The "concentration" of enzymes is calculated by Wohlgemuth from the square of the digested column of coagulated protein or starch, or the square of the number of cubic centimeters of alkaline solution required for the neutralization of fatty acids.

The pancreatic juice possessed the greatest proteolytic, lipolytic and amylolytic power when secreted on food rich in fat. The enzymatic activity of the juice was less when its flow was stimulated by food containing much protein or carbohydrate.

Recently Balo and Lovas (1933) studied the relative amounts of trypsin, amylase and lipase (glycerol extracts prepared by the method of Wilstatter and Waldschmidt-Leitz) in the pancreatic gland of persons who had died of various diseases (70 cases). A parallelism

\*Department of Physiology, McGill University.  
Submitted January 25, 1935.

was generally found between the concentrations of the three enzymes. In sepsis, however, the tryptic activity of the pancreatic extract was greatly decreased, while the amylolytic and lipolytic activities remained normal. In two cases of fat necrosis of the pancreas the content of lipase was increased. It must not be forgotten that the authors were working not with the pancreatic juice but with extracts of the glandular tissue.

These investigations establish the fact that in the pancreatic gland of a carnivorous dog or an omnivorous man the three principal enzymes are always secreted in parallel concentrations.

No reference could be found in the available literature concerning the secretion of pancreatic enzymes in parallel concentrations by the herbivorous animals (*cf.* Mangold, 1929). During investigation of the pancreatic secretion in the rabbit (Baxter, 1931, a and b) this problem presented itself and became the subject of a special study, which is reported here.

### METHODS

Rabbits were anaesthetized with urethane, 1 gr. per. kg. of 20 per cent solution being injected intravenously. In some experiments the animals during brief ether anaesthesia were decerebrated or decapitated. The pancreatic duct was cannulated and the pancreatic juice was collected in half-hourly or hourly samples. Since the pancreatic gland of the rabbit secretes spontaneously, in many experiments in order to obtain more uniform results the pylorus and the bile duct were ligated.

For determination of the proteolytic enzyme Mellanby's (1912) method of coagulation of caseified milk was used. This method is based on the assumption that all proteolytic ferments coagulate milk, provided the calcium content of the milk be adequate. The protrypsin was activated by the enterokinase solution prepared by grinding 30 gr. of intestinal mucosa to which 100 c.c. of water were added. Each cubic centimeter of pancreatic juice was activated by incubation with 2 c.c. of enterokinase solution on a water bath (40° C.) for one hour. 0.1 c.c. of the activated juice was added to 2 c.c. of milk solution and incubated at 40°

C. The first appearance of flocculent particles was taken as the end-point. The time required for the coagulation of the milk by a given sample of pancreatic juice was converted into an arbitrary value in units; these were in inverse relationship to the time of coagulation.

The amylolytic power of the juice was determined by the method of Waksman (1920). This enzyme was not activated in this series of determinations.

For the determination of the lipolytic activity Mellanby's (1925) method was adopted. One series of determinations was performed on inactivated juice, another on a juice activated by bile.

### RESULTS

Figure 1 represents an experiment in which 1.5 mg. of pilocarpin hydrochloride were twice injected intravenously. This drug augmented the volume of the spontaneous secretion and very distinctly increased the enzymatic power of the juice. This parasympathomimetic effect of pilocarpin may be explained by the fact previously established (Baxter, 1931 *b*) that the vagus is a secretory nerve of the pancreas. Faradic stimulation of the vagus increases the pancreatic secretion in the rabbit and raises the digestive power of the juice.

Whereas the concentrations of trypsin and lipase run closely parallel with each other both after the first and after the second injection of pilocarpin, the rise of the amylolytic power of the juice after the first administration of the drug is relatively smaller than after the second. It would be more correct, however, to attribute this fact not to actual dissociation of the discharge of enzymes from the glandular cells but rather to the imperfection of our methods of enzyme determination, to the destruction of one enzyme by another, or perhaps to the different inorganic composition of the pancreatic juice secreted under various conditions. However, without further investigation, necessitating the most accurate methods of enzyme determination, it is impossible to ascertain the extent of this parallelism between the different pancreatic ferments.

The second injection of 1.5 mg. of pilocarpin increased the volume of the secretion practically to the same degree as did the first, but it failed to produce the same rise in the enzymatic power of the juice as occurred after the first injection. This probably was due to exhaustion of the stores of zymogen granules in the cells of the pancreatic gland.

Figure 2 shows another experiment in which the flow of the pancreatic juice and its digestive power were likewise increased by two injections of pilocarpin of 1.5 mg. each. Only trypsin and lipase were determined in this experiment. The latter was activated by bile. The results of the lipase determination are expressed in cubic centimeters of 0.01 N NaOH as a direct measure of the lipoclastic power of the juice. The relations between the trypsin and the lipase during the course of this experiment remained in general the same as in the previous experiment when the lipase was not activated. Every rise and fall of the trypsin was followed by a rise and fall of the lipase. But the absolute lipolytic power of the juice owing to its activation by bile was much higher in this experiment than in the preceding. The highest figure for the activated lipase was 24 c.c. of 0.01 N NaOH solution, whereas the highest lipoclastic power of the inactivated juice was only 12 c.c. of the same solution.

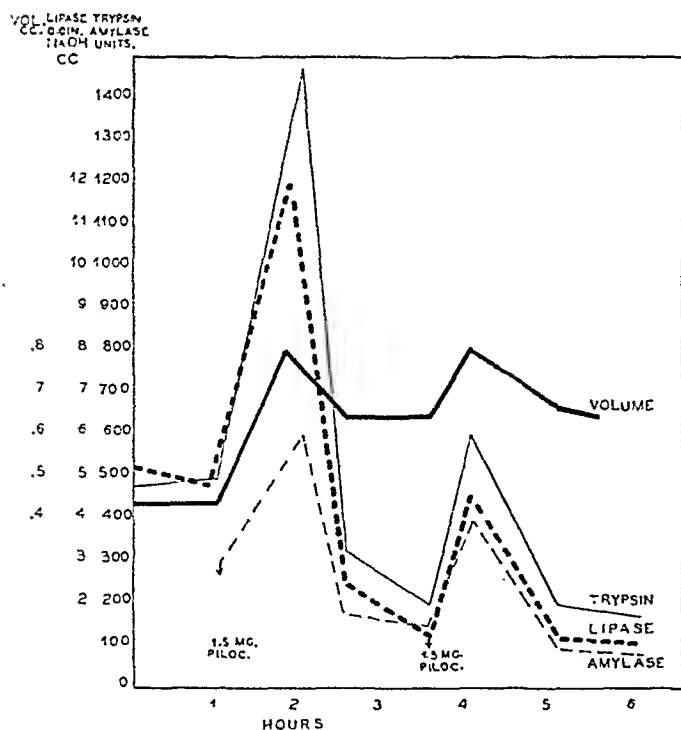


Fig. 1.

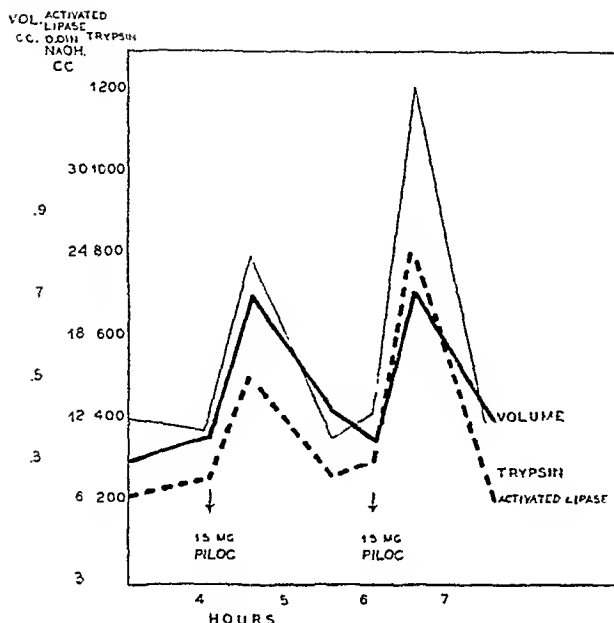


Fig. 2.

### DISCUSSION

The structure of the pancreatic gland is very uniform. There is only one kind of secretory cell, containing the zymogen granules. Therefore, it is very probable that one and the same acinous cell elaborates all three of the principal pancreatic enzymes. Nothing, however, is known about the intimate mechanism involved in the formation and secretion by the acinous cells of the pancreas of these or indeed any of the half dozen pancreatic enzymes. A special experimental and clinical study of the enzymatic activity of that part of the pancreatic gland which is in the service of the external secretion of the organ, is highly desirable. However, even the imperfect knowledge which we now possess of the interrelations between different enzymes of the pancreatic juice may have an important practical value.

One of the methods employed in determining the functional activity of the acinous tissue of the pancreatic gland in patients is the estimation of the enzymatic power of the aspirated duodenal contents. There is hardly any diagnostic procedure more uncertain than this, because the duodenal contents may include up to fifteen enzymes and activators, each of which may interfere with the action of the others. The task of the clinician might be simplified somewhat if the parallel concentration of the three principal enzymes of the pancreatic juice were taken into consideration. This being admitted, it would be sufficient for the estimation of the functional activity of the pancreas to determine the power of only one of the many enzymes of the pancreatic juice. Katsch and von Friedrich (1922) on the other hand advise determination of all three enzymes in the duodenal contents aspirated after injection of a small amount of ether into the duodenum of the patient. According to these authors ether produces a secretion of pancreatic juice in which the three enzymes do not occur in parallel concentrations. But they themselves consider this an unphysiological method of producing pancreatic and other duodenal secretions—with which statement probably hardly anybody will disagree.

Let us discuss briefly the relative diagnostic value of determining each of the three chief pancreatic enzymes in the duodenal contents.

Although the *succus entericus* contains an *amylase*, the action of the latter is very weak. Therefore it does not play any essential part in the intestinal digestion of carbohydrates (cf. Babkin, 1928, p. 768, and Oppenheimer, 1925, vol. 1, p. 725), and can hardly interfere with the determination of the pancreatic *amylase*. But the possibility that saliva, which possesses a strong *amylase*, may be present in the duodenum, cannot be excluded. Certain data indicate (cf. Oppenheimer, 1925, vol. 1, p. 424) that salivary *amylase* is not all destroyed by the acid of the gastric juice, and some of it may be reactivated in the duodenum, so that one *amylase* may be taken for the other. Further difficulties arise because, according to Kuhn (1925) and Reichel (1932), both the salivary and the pancreatic *amylase* belong to one and the same group of  $\alpha$ -*amylase*. Purr (1934) believes that the salivary *amylase* belongs to the  $\alpha$  type, whereas the pancreatic *amylase* is a mixture of the  $\alpha$  and  $\beta$  types. But the difference in this respect between the two preparations investigated by Purr might be due to the fact that in one case he used a true secretion, i.e. human saliva, while for the study of the pancreatic *amylase* he employed acetone-ether-dried pig's pancreas. Therefore the presence of tissue enzymes in this latter preparation is highly probable. In this connection it is worth while to mention that *beta*-*amylase* may be extracted from rat's liver and from many plants. All this makes the differential determination of the salivary and pancreatic *amylases* in the duodenal contents very difficult, and hence the estimation of the functional capacity of the pancreatic gland uncertain.

It is true that the *pancreatic lipase* plays a predominant role in the intestinal digestion of fat, because the *lipase* secreted by the intestinal mucosa is far less active. However, the presence of the latter in the duodenal contents cannot be ignored.

According to Waldschmidt-Leitz and Schöffner (1926) the *pancreatic erepsin* and the *intestinal erepsin* are identical (cf. Oppenheimer, 1926, vol. 2, pp. 875 ff.). On the other hand Leberton and Mocorona (1931) deny the presence of erepsin in the pancreatic juice. They showed that of the five enzymes found by Wilstatter, Waldschmidt-Leitz and their school in the extracts of the pancreatic gland, namely prokinase, proteinase, carboxypolypeptidase, and two ereptic enzymes, i.e. aminopolypeptidase and dipeptidase, only the first three enzymes pass into the *pancreatic juice*. The ereptic enzymes are endocellular and are present only in the extracts.

We come now to the discussion of trypsin determination. Since the time when Shepovallnikov (1899), working in Pavlov's laboratory, discovered *enterokinase*, it has been known that the intestinal juice does not digest coagulated protein. It dissolves fibrin, but this requires from 14 to 16 hours, whereas the activated pancreatic juice does it in a few minutes. From native proteins casein and gelatin are also split by the intestinal juice, which action is ascribed by Waldschmidt-Leitz and Schöffner (1926) to the *intestinal trypsin*. This effect, however, is very weak. Therefore, it seems that the determination of trypsin in the duodenal contents is the most reliable method for the



estimation of the external secretory function of the pancreatic gland. This is evident from the fact that pancreatic trypsin will attack coagulated protein in an alkaline medium, which no other enzyme of the gastro-intestinal tract could do.

The old Mett's method (digestion of coagulated egg-white), somewhat modified, still may be recommended as a suitable clinical method for determining the tryptic activity of the pancreatic juice. Although it cannot be considered so accurate as other more elaborate methods of protease determination, its advantage lies in its simplicity and reasonable dependability. The application of Mett's method in clinical

practice was recently reconsidered by Patterson and Adler (1932) and found by them to be quite suitable.

#### SUMMARY

(1) The parallel concentration of trypsin, amylase and lipase in the pancreatic juice of the rabbit is demonstrated. These data are in conformity with those obtained from analogous studies by previous investigators of human and canine pancreatic juice.

(2) The possible application of these data to the practical problem of functional diagnosis of the external secretion of the pancreatic gland is discussed.

My thanks are due to Dr. B. P. Babkin for his interest in this problem, and for his helpful advice and criticism during the progress of the work.

#### REFERENCES

- Babkin, B. P.: *Trans. Military Medical Academy, St. Petersburg*, 9:98, 1904.  
 Babkin, B. P.: *Die äussere Sekretion der Verdauungsdrüsen*. 2nd ed., Berlin, 1928.  
 Babkin, B. P., and N. P. Tichomirov: *Hoppe-Seyler's Zeitschr. f. physiol. Chemie*, 62:468, 1909.  
 Baló, J., and L. Lovas: *Virchow's Arch.*, 288:326, 1933.  
 Baxter, S. G.: *Amer. Jour. Physiol.*, 96:343, 1931 (a).  
 Baxter, S. G.: *Amer. Jour. Physiol.*, 96:349, 1931 (b).  
 Katsch, G., and L. von Friedrich: *Klin. Wochenschr.*, 1:112, 1922.  
 Kuhn, R.: *Liebig's Ann. d. Chem.*, 443:1, 1925.  
 Leberton, E., and F. Mocoroo: *C. R. de l'Acad. des Sci., Paris*, 192:1942, 1931.  
 Mangold's: *Handbuch der Ernährung und des Stoffwechsels der Landwirtschaftlichen Nutztiere*, vol. 2, pp. 230:258, Berlin, 1929.  
 Mellanby, J.: *Jour. Physiol.*, 45:345, 1912.  
 Mellanby, J.: *Jour. Physiol.*, 60:55, 1925.  
 Oppenheimer, C.: *Die Fermente*, 5th ed., vol. 1 and 2, Leipzig, 1925 and 1926.  
 Patterson, J., and J. Adler: *Brit. Jour. Exp. Pathol.*, 13:72, 1932.  
 Purr, A.: *Biochem. Jour.*, 28:1141, 1934.  
 Reichel: *Dissertation, Deutsch. Techn. Hochschule, Prag*, 1932. (Quoted from Purr).  
 Sawitsch, W. W.: *Zentralbl. f. d. ges. Physiol. u. Pathol. d. Stoffwechsels*, no. 1, 1909.  
 Sheporainikov, N. P.: *Thesis, St. Petersburg*, 1899.  
 Waksman, S. A.: *Jour. Amer. Chem. Soc.*, 42:293, 1920.  
 Waldschmidt-Leitz, E., and A. Schäffner: *Zeitschr. f. physiol. Chemie*, 151:31, 1926.  
 Wohlgenuth, I.: *Berl. klin. Wochenschr.*, p. 47, 1907.

## ABSTRACTS

C. G. BURN, New Haven, Conn.

*Postmortem Bacteriology. Jour. Infect. Dis. Pages 388-403.*

This very important subject is discussed in two very interesting articles. The bodies studied were subjected to a temperature of 10° C. (50° F.) within a short time after death and were kept there until the necropsy was performed. Opportunity was not at hand for study of bacterial invasion during the first hour after death or at the time of death. It was found that a large group of pathogenic and nonpathogenic bacteria failed to invade the tissues after death, even though ample opportunity was given for such invasion. Organs and body fluids, however, disclosed a high incidence of bacterial growth at necropsy. Lungs, kidneys, liver, spleen and blood from the heart show frequency of growth in the order named. *B. coli*, staphylococci, *Clostridium welchii*, and nonhemolytic streptococci are the more frequently isolated strains of bacteria. Other types isolated are usually associated with disease states within the body. "No significant differences can be demonstrated in either the frequency or the kind of bacteria isolated from organs, post mortem between the first and forty-eighth hour after death." The quantity of organisms, their location within the body, and the time between death and necropsy may be important factors influencing postmortem invasion.

J. Arnold Bargen, Rochester, Minn.

F. D'HERELLE AND T. L. RAKIETEN, New Haven, Conn.

*Mutations as Governing Bacterial Characters and Serologic Reactions. Jour. Infect. Dis. Pages 313-338.*

The number of bacterial mutants arising from a single strain under action of phage is indefinite. *Salmonella enteritidis* was used in this study. All mutants differ in some precise characteristics. The transformations are not stages in the life cycle of the organism. Bacteria can be made to carry phage, thus creating symbiosis between the separable entities, a bacterium and a phage. In such a symbiosis, each of the components adapts itself to the action of the other; the phage as well as the bacterium undergoes modifications in its characters.

The study of bacterial mutants leads to important immunologic data. The pathogenicity of bacteria is governed by mutations under the action of phage. Some mutants from an original pathogenic bacterium are completely avirulent, while others are fully as virulent as the original strain. There may be all manner of intermediaries, including those provoking a chronic disease.

In a diseased organism not only does the host undergo modifications, leading to production of antibodies, but at the same time the invading bacteria, through the action of phage, undergo modifications, leading to what appears to be increased sensitivity to the action of complement.

J. Arnold Bargen, Rochester, Minn.

MANN, FRANK.

*Hepatic Function in Relation to Hepatic Pathology; Experimental Observations. Ann. of Int. Med., VIII, 432, Oct., 1934.*

An imposing array of hepatic function tests is all but consigned to discard in an account of experimental work done on the liver.

If regret be felt for the threatened fatality to diagnostic procedures, some consolation may be winnowed from the wreck in the knowledge that physical restoration of removed or injured liver tissue went on at an extent not shared by most other organs and exceeded by none. It affords strange reading to be told that the restorative activity of the liver "makes it difficult to produce, experimentally, a decrease in the functioning hepatic tissue to such an extent that the hope would be justified that the physiological activity had been reduced to an amount that could be measured."

Partial removal of the liver, even as much as 70 per cent, was followed by rapid and complete restoration of liver tissue. Several weeks' administration of carbon tetrachloride were required to produce a condition analogous to cirrhosis in the human liver. The mechanical obstruction of bile flow injures only one function of the liver unless maintained for months. It appears that only a combination of the various methods for damaging liver tissue or impairing function will make such damage or impairment permanent. Concerning the functional attributes of the liver emphasis is placed on (a) the normal liver has a capacity much in excess of the normal needs of the body; (b) the functional capacity of the liver depends on a number of factors and changes with great rapidity; (c) impairment of one function may not impair any other function of the liver; there seems to be even a dissociation of the functions of the liver; (d) singularly, despite this dissociation of its own functions, there is an association or correlation of liver functions with those of other organs which makes difficult delineation of hepatic factors; (e) normal hepatic functions can be carried on by a very small bit of normal liver tissue.

In studying liver function bile ranks as the oldest. Cholesterol, bile pigments and bile acids are the most important of these; not enough of the source or significance of cholesterol is known to warrant its determination helpful as a function test. Of bile pigments bilirubin has been thought to be the best index to liver injury, but its significance in estimating function is modified by (a) its origin from hemoglobin. (b) Much of the total bilirubin found

in the body is of extra-hepatic origin. (c) All of the body bilirubin could be excreted by a very small amount of liver tissue. (d) Tests for bilirubin estimate the amount retained in the blood, but do not furnish adequate data for estimation of hepatic damage. Bile salts are found in traces only in health and are not definitely detectable in the blood. The administration of large amounts result in little or no increase in the excretions or the blood. Bile salts are not formed when the liver is removed. The liver both forms and destroys bile salts. Concentrations of bile salts in the blood and urine are significant of liver injury, but it is doubted if their estimation can be used as a hepatic function, chiefly because the liver both makes and destroys bile salts.

Certain dyes are largely disseminated by the liver. The rate the liver removes such a dye is an index to that function alone and is not a physiological measure of other liver functions. Some pathological changes were found to bear no relationship to dye excretion; this is especially true of scirrhus changes.

Considering the liver in relation to carbohydrate metabolism and the tolerance tests based on this function, attention is called to the fact that the fate of dextrose depends on so many extra-hepatic factors that changes in glucose tolerance cannot be considered indicative of impaired hepatic function. The glycogen content of a normal liver may vary as much as from 1 to 20 per cent.

Since muscles can make glycogen from levulose, it follows that levulose might be utilized where there was little liver function left. Therefore, levulose tolerance tests to measure liver injury are not thought worth while.

Galactose is a sugar largely used by the liver, but there exists a wide difference in the rate of its use in normal animals; its use as a sugar-function test would seem useless.

A study of the nitrogen partition in blood and urine in animals and the effect of liver injury on these phases of metabolism was thought to indicate that hepatic injury cannot be quantitated by changes in nitrogenous excretion.

The author concludes that no quantitative relationship could be found between the amount of functioning liver tissue and the capacity of such tissue to maintain any of the known functions of the liver. That destruction of liver tissue short of death an animal produces little or no changes in those physiological processes which are abolished by total removal of the liver.

Virgil E. Simpson, Louisville.

## SECTION III—Nutrition

### MILK

By

HORACE W. SOPER, M.D.\*  
ST. LOUIS, MISSOURI

A REVIEW of the recent literature concerning milk as a food for human beings reveals many interesting observations. Man appears to be the only mammal which habitually consumes milk after the period of lactation has ceased.

Crumbine and Tobey (1) in their excellent monograph on milk state that as a result of their researches it was used as a food 4000 years B.C. The Aryans of Central Asia were the first herdsmen, and honey and milk was a prized drink. Goats' milk and mares' milk were consumed by the ancient Greeks. The ancient Egyptians depicted the heavens as a cow with a full udder.

Most authorities on nutrition, particularly McCollum (2), consider milk a food for which there is no adequate substitute. He advises that one quart of this "protective food" a day should be consumed. He points out that the inhabitants of the wet regions in southern Asia subsist on a diet of rice, soy beans, sweet potatoes and many other vegetables. Bamboo sprouts and other leafy vegetables are eaten in large quantities. They have no herds and do not consume milk. He states that these people are better developed physically, have more capacity for work and endurance, that they escape the skeletal defects in childhood, and have the finest teeth of any race in the world. In the dryer regions of the world, the people consume large amounts of sour milk. Metchinkoff, forty years ago, became interested in the large number of centenarians among the Bulgarian peasants. He attributed their longevity to the life-long habit of drinking sour milk, fermented by the *lacto-bacillus Bulgaricus*.

Timothy Leary (3) in his work on athero-sclerosis states that man is the only animal who ingests eggs and milk throughout its lifetime. Man is the only animal, as far as is known, who dies in early life from coronary sclerosis and which acquires athero-sclerosis almost universally in advanced life. He was impressed with the high content of lipoids in atheromatous aortae. He conducted a series of experiments—feeding rabbits cholesterol. He also studied cases of human coronary sclerosis. Cholesterol is the only sterol found in animal bodies. It forms the framework of all animal cells. It combines with fatty acids to form esters. In our dietary, eggs, milk, and pork fats are the main sources of supply. He concludes that the lesions of human athero-sclerosis can be reproduced in the rabbit by feeding cholesterol. The inheritance of

a poor cholesterol metabolism appears to be associated with the tendency to early death from coronary sclerosis. Leary points out that the custom formerly used of feeding diabetics diets excessively rich in fats, resulted in a great increase of athero-sclerosis in the subjects.

Joslin (4) suspects high cholesterol blood content as the etiological factor in cataract and arteriosclerosis. He emphasizes the importance of keeping the fat in normal limits in diabetics, at least under 230 mg. of cholesterol per 100 c.c. of blood.

Rabinowitch (5) calls attention to the relationship between the carotin and cholesterol content in the blood of diabetics and arteriosclerosis.

Milk is an important constituent of the alkaline-ash diet as emphasized by Sansum and his co-workers.

Dental caries, root infections, and pyorrhea form too large a subject to attempt elucidation here. Bunting concludes his study of the subject as follows: "To this end it is highly desirable that group studies be made in which the allied sciences of chemistry, nutrition, bacteriology and dentistry may be correlated in a truly scientific attack on this difficult and important problem in human welfare." Can milk be implicated as an etiologic factor? Ernst A. Hooton (7), Professor of Anthropology at Harvard University, in a broad survey of "The Teeth of Apes and Men," a recent article in the "Scientific Monthly," concludes that "foci of infection in teeth undermine the entire bodily health of the species and that degenerative tendencies in evolution have manifested themselves in modern man to such an extent that our jaws are too small for the teeth which they are supposed to accommodate." "I firmly believe that the health of humanity is at stake and unless steps are taken to discover preventatives of tooth infection and correctives of dental deformities, the course of human evolution will lead downward to extinction." Professor Hooton points out that primitive man was singularly free from tooth infection with the single exception of the Rhodesian man—equipped with the longest face, the largest palate, and the worst teeth of antiquity; that examination of the skulls of savage races reveals that they did not suffer from dental caries and apical abscesses. The teeth are usually found to be worn down by attrition. It is notable that such people were not consumers of goat's or cow's milk. Professor Hooton is greatly impressed with the fact that nine out of ten school children in the United States have decayed teeth.

\*From the Soper-Mills Clinic.  
Submitted January 9, 1935.

McCollum (2) emphasizes the necessity of the presence of vitamins "D" and "C" and adequate amounts of phosphorus and calcium in the dietary for the development of good teeth.

The bacterial flora of the intestine of breast fed infants shows a preponderance of the bacilli known as *lacto-acidophilus*. The intestine of the adult abounds in proteolytic bacteria.

Bunting (8), Professor of Oral Pathology in the University of Michigan, came to the following conclusions after five years research work. "Dental caries is dependent on the infestation of the mouth by specific types of bacteria capable of producing acids by the fermentation of residual carbohydrate food materials and capable of living in their own products. *Lactobacillus Acidophilus* is the organism always found in dental caries. It is never found in the mouths of persons free from dental caries. It is also found in the intestinal tract of carious persons." Bunting believes that the character of the foods eaten by civilized people is a great factor in the production of dental caries. Primitive peoples living on simple foods are free from caries until they come in contact with civilization.

Kopeloff, Blackman and McGinn (9) examined the feces of 208 adult inmates of an institution and found *Bacillus Acidophilus* in 62% of them. No dietary restrictions were imposed. They state that constipation was not a factor.

Roettger (10) states that he and his associates have demonstrated the occurrence of high acid-producing bacteria in dental caries, which proved to be streptococci.

Rosenow discovered the presence of streptococci in apical abscesses and demonstrated their relationship to gastric and duodenal ulcer, appendix and gall bladder infections.

An important report (11) on the milk supply of London was recently made. It appears that the milk is gathered in the country and transported to London in large glass-lined tanks, each holding 3000 gallons. These tanks contain milk from different herds. The first examination of ten road and rail tanks showed all contained living virulent tubercle bacilli. The latest figures for tank milk show that out of forty-one samples, thirty-four or 83% contained tubercle bacilli. After pasteurization and examination of two hundred and eighty-two samples purchased over the counter, nine or 3.2% contained tubercle bacilli.

In the cities of Edinburg, Glasgow, Aberdeen and Dundee (12), specimens of pasteurized milk as retailed gave a figure of over 5% of samples that contained tubercle bacilli. In England, 45% of tuberculosis of the cervical glands, 47% of lupus, 30% of tuberculosis of the meninges, and 18% of that of bones and joints have been found to be due to the bovine bacillus. In Scotland the corresponding figures are 73, 53, 12 and 42.

The work of Saunders (13), *et. al.*, in "Infection in Gastric and Duodenal Ulcer" is of extreme importance. Their conclusions are as follows: "The organism studied by us is found in milk from cows suffering with mastitis, and is not identical with any other type of streptococcus tested. It will stand the heat of pasteurization, it does not live in bile media of the lowest dilutions, and is not affected by a high acidity. It is the only factor which can explain the epidemic-like

occurrence of ulcer in children from one to six months of age as reported by Helmholtz (14). An identical organism has been isolated from thirty resected ulcers of the stomach and duodenum, and has been proved identical with three others isolated from cows milk, and is not identical with any other streptococcus tested. Following surgical duodenal drainage in dogs, 14 typical ulcers were found in five of the group of ten fed cultures of the organism, and only 2 erosions in two of the control group of nine not fed the organisms."

"Place and Sutton (15) have reported an epidemic of arthritic erythema or Haverhill fever which was traced to the use of raw milk. They have isolated an organism (*Haverhillia multiformis*) found in the blood and fluid of involved joints of patients suffering from the disease."

"G. M. Fyfe (16) reports a Milk-Borne Sonn  dysentery epidemic affecting 150 persons."

Rosenow (17) reports an institutional outbreak of poliomyelitis in a midwestern college apparently due to a streptococcus in raw milk. The epidemic ceased to spread after discontinuance of the use of unpasteurized milk and cream.

Rosenow, Rosendaal, and Thorsness (18) have reported the results of their investigation in the Minnesota epidemic of poliomyelitis. They found a streptococcus isolated from raw milk at the time of the epidemic that was identical with that isolated in cases of poliomyelitis in human beings and monkeys, in its thermal death point, in its morphology and cultural characteristics, in its immunologic properties, and in its cataphoretic velocity. They also found the poliomyelitis streptococcus in several samples of pasteurized milk.

Much work has been done on the subject of pathogenic bacteria in milk by Ayres and Johnson (19) who found that pasteurized milk soured due to the development of lactic acid bacteria which had survived pasteurization or due to reinfection. They also state that the relative proportion of groups of peptonizing lactic acid and alkali or inert bacteria in pasteurized milk is about the same as in raw milk. In later articles they point out that the "majority" thermal death point is quite different from the "absolute" thermal death point of bacteria (20) and (21). Prucha (22) found that pasteurization reduced the bacteria count in milk in general about 99% but under certain conditions, the milk became heavily contaminated with bacteria that had resisted pasteurization temperature. The way in which the milk was handled had much to do with the effectiveness of pasteurization. He found that no spore-forming organism was completely destroyed at 62.2° C. (144° F.) (23). Bacteria which may survive pasteurization are classified as follows:

1. Heat resistant non-spore-forming bacteria
2. Thermophilic bacteria
3. Streptococci
4. Non-thermophilic spore-forming bacteria.

The cow is essentially an unclean animal. Efforts to sterilize the udder are unavailing. The skin cracks and becomes eczematous and the scabs fall into the milk. Mastitis is a frequent development. Despite all strenuous efforts and precautions, the best milk delivered from the dairies continues to show the presence of pathogenic bacteria.

## THE EVAPORATED CANNED MILK

Marriott (24) in 1929 pointed out the great advantages in feeding this milk to infants and young children. He states "that a large or tough curd could not be formed in the stomach or intestine from evaporated milk. There are good reasons for supposing that a fine curd from milk used for infant feeding is desirable. The protein is more completely digested when small curds are formed in the stomach, bacteria are not enmeshed and removed from the influence of the bacterial acid gastric juice." Furthermore, he fed 752 young infants evaporated milk and concluded that it is the full equivalent of pasteurized or boiled whole cow's milk. He had splendid results in feeding the evaporated milk to premature infants. Following Marriott's leadership, pediatricians all over the country are practically unanimous in supporting this opinion. The literature on the subject is voluminous. I mention Brennemann (25), Lowenburg (26), Koch and Samuels (27), Tobey (28), Kerley (29), Cutler (30), Jeans and Stearns (31), and many others. Todhunter (32), Kramer, Latzke and Shaw (33), demonstrated that evaporated milk gave a higher calcium balance than did fresh milk and pasturized milk.

In the year 1929, Crumbine and Tobey (1) asserted that evaporated milk was "The most nearly perfect food." "Because of its many sanitary and economic advantages, this is the milk supply of the future, though it is improbable that evaporated milk will supersede whole milk supplies in our large cities in the next few years." "Sometime ago, the late Dr. Hermann M. Biggs, State Commissioner of Health of New York, prophesied that eventually all milk would be in the concentrated form. His forecast has not yet come true, but as the public comes to appreciate the safety, uniformity, stability, digestibility, nutritional quality, convenience, and inexpensiveness of the concentrated milks, this prophecy of Dr. Biggs' may eventually be more nearly accomplished."

Davidson, Biguria and Guild (34) conclude their study of the use of evaporated milk as follows: "With regard to the influence on gastric acidity and motility, our experiments seem to indicate that evaporated milk, diluted and undiluted, may be used as well as milk and milk and cream mixtures, in the treatment of conditions that require a bland or semi-bland diet." Ross (35) treated a series of cases of peptic ulcer and concludes "that the use of evaporated milk in ulcer diets is a further advance because it is easily digested, contains no lactic acid bacilli, and it is sterile." Todhunter (32) reports that young rats on a vitamin G free diet were fed diluted evaporated milk, pasteurized milk, and whole cooked egg, as sources of vitamin G. Of diluted evaporated milk 10.1 c.c. per week, of pas-

teurized milk 9.3 c.c. per week, and of egg 5.2 grams per week were found to give "unit growth" of 24 grams over a period of eight weeks. The vitamin G values found for market milk and for evaporated milk diluted according to the directions on the container are, therefore, substantially alike.

About four years ago, I became convinced that raw as well as pasteurized milk contained pathogenic bacteria and advised boiling milk and cream. In time, I employed the evaporated milks particularly in cases of gastric and duodenal ulcer, ulcerative colitis, catarrhal colitis, etc. The results were so satisfactory that I prescribed the canned evaporated milks exclusively in my diet-lists for such conditions. Ulcers healed more quickly and recurrences were less frequent. Ulcerative colitis patients responded especially well and relapses which formerly were so common are now rarely encountered. Many cases of catarrhal colitis are quickly corrected by this simple change in dietary habits. A complete report of my clinical experience with the evaporated milks will be made later.

Recently I submitted to the Gradwohl Laboratory, 13 specimens of milk, representing the different St. Louis dairies. These were cultured according to the United States Health Standards.

5 of the specimens showed the presence of streptococcus viridans

4 showed staphylococcus albus

2 showed acidophilus

1 showed encapsulated streptococci which failed to grow in cultures

1 showed almost a pure culture of pneumococci-like organisms.

The tremendous importance of the problems involved is obvious, particularly so in view of the fact that all our municipalities are engaged in strenuous but futile attempts to secure a pure milk supply.

*The following conclusions appear to be justified:*

1. Research into the habits of the people of ancient as well as modern civilizations reveals that they were consumers of milk and all suffered from dental caries.

2. Raw milk is unfit for human consumption.

3. Pasteurized milk as it reaches the consumer, usually contains pathogenic bacteria and is not to be relied upon as a safe food.

4. The canned evaporated milk is sterile, more easily digested, keeps in the tin indefinitely without refrigeration, and contains all the elements of nutrition desirable in milk. Furthermore, its general use by the public would mean a tremendous economic gain.

6. Should the experimental work of Bunting and that of Timothy Leary receive general confirmation, it would indicate a complete readjustment of our alimentary habits.

## REFERENCES

1. Crumbine, Samuel J., and Tobey, James A.: "Most Nearly Perfect Food," Williams & Wilkins Co., 1929.
2. McCollum, E. V.: "Food, Nutrition and Health," Third Edition, August, 1933.
3. Leary, Timothy: "Experimental Athero-sclerosis in the Rabbit compared with Human (Coronary) Athero-sclerosis." *Arch. Path.*, 17:453, April, 1934.
4. Joslin, E. P.: "Fat and the Diabetic." *New England J. Med.*, 209:519, September 14, 1933.
5. Rabinowitch, I. M.: "Observations on the Significance of the Cholesterol Content of the Blood Plasma in Diabetes Mellitus." *Canad. M. A. J.*, 28:162, February, 1933.
6. Hooton, Ernst A.: "Apes, Men and Teeth." *Scientific Monthly*, p. 24, January, 1934.
7. Bunting, R. W.: "Recent Developments in the Study of Dental Caries." *Science*, 78:419, November 10, 1933.
8. Kopeloff, Blackman and McGinn: "The Incidence of Lacto-bacillus Acidophilus in Adults." *Jour. Infet. Diseases*, Vol. 50, p. 426.
9. Rettger, Leo F.: "Dental Caries." *J. A. M. A.*, Vol. 102, No. 14, April 7, 1934.
10. London Letter: *J. A. M. A.*, Vol. 101, No. 22, p. 1737, November 25, 1933.
11. London Letter: *J. A. M. A.*, Vol. 102, No. 9, p. 708, March 3, 1934.
12. Saunders, Edw. Watts: "Infection in Gastric and Duodenal Ulcer." *Am. Jour. Med. Sc.*, Vol. CLXXXVII, No. 2:743, February, 1934.
13. Helmholtz, H. F.: *Arch. Pediat.*, 26:661, 1909.
14. Place, Edwin H., and Sutton, Lee E.: *Arch. Int. Med.*, Vol. 54, No. 5, November, 1934.

16. Fyfe, G. M.: *Jour. Hyg.*, 26:271, August, 1927.
17. Rosenow, Edw. C.: *Jour. Infect. Dis.*, Vol. 50, p. 377, 1932.
18. Rosenow, Edw. C.; Rosendaal, Hendrik M., and Thorsness, Edwin. T.: "Acute Poliomyelitis. Studies of Streptococci isolated from Throats and Raw Milk in Relation to One Epidemic." *Jour. Pediat.*, Vol. 11, No. 5, p. 568, May, 1933.
19. Ayres and Johnson: *Centr. Bakt. U. Path.*, 2:40, 109-131, 1913.
20. Ayres and Johnson: U. S. Dept. Agr. *J. Agr. Res.*, 2:321, 1914.
21. Ayres and Johnson: *Jour. Bact.*, 9:279, 1934.
22. Prucha: *Am. Jour. Pub. Health*, 17:356, 1927.
23. Prucha: *Ann. Rep. Ill. Ag. Exp. Sta.*, 158, 1927.
24. Marriott, W. McKim: "An Experimental Study of the Use of Unsweetened Evaporated Milk for the Preparation of Infant Feeding Formulas." *Arch. Pediat.*, XLVI, 46:135, March, 1929.
25. Brennemann, Jos.: "The Curd and the Buffer in Infant Feeding." *J. A. M. A.*, 92:364, February 2, 1929.
26. Lowenburg, Harry: "Clinical Experience with Evaporated Milk as a Source of Food Supply in 175 Artificially Fed Sucklings." *Medical Times*, 1929.
27. Koch, Fred C., and Samuels, Leo. T.: "The Relative Quantities of the Heat Stable and Heat Labile Fractions of Vitamin B. in Raw and Evaporated Milk and Eggs." *Jour. Nutri.*, Vol. 307:324, 1932.
28. Tobey, James A.: "Recent Clinical Experiences with 3,800 Infants on Evaporated, Powdered and Condensed Milk." *Arch. Pediat.*, L:153-191, 1933.
29. Kerley, Chas. Gilmore: "Evaporated Milk in Infant Feeding." *Arch. Pediat.*, XLIX:22:26, 1932.
30. Cutler, Oran J.: "Antigenic Properties of Evaporated Milk." *J. A. M. A.*, 92:964, 1929.
31. Jenns, Phillip C., and Stearns, Genevieve: "Growth and Retention of Calcium, Phosphorus, and Nitrogen of Infants Fed Evaporated Milk." *Am. Jour. Dis. of Children*, Vol. 46, p. 69, July, 1933.
32. Todhunter, E. N.: "A Comparison of Vitamin G. Values of Pasteurized Milk, Evaporated Milk and Eggs." *Jour. Am. Dietetic Assn.*, Vol. VIII, No. 1, p. 42, May 9, 1932.
33. Kramer, M. M.; Latzke, E., and Shaw, M. M.: "A Comparison of Raw, Pasteurized, Evaporated and Dried Milks as Sources of Calcium and Phosphorus for the Human Subject." *Jour. Biol. Chem.*, 79:283, 1928.
34. Davidson, P. G.; Biguria, Fernando, and Guild, Ruth: "The Use of Evaporated Milk in Digestive Disorders, Particularly Peptic Ulcer." *Jour. Am. Dietetic Assn.*, Vol. IX, No. 6, March, 1934.
35. Ross, John B.: "The Treatment of Peptic Ulcers with an Evaporated Milk Diet." *Ill. Med. Jour.*, Vol. LXIII, No. 1, January, 1933.

## ABSTRACTS

RIVERS, ANDREW B.; STEVENS, J. ARNOLD, AND KIRKLIN, B. R.

*Diverticula of the Stomach. S. G., and O., 60:106-113, Jan., 1935.*

In a short but rather complete paper the authors discuss the disease and present reports of 14 proved cases (ten removed at operation and four obtained at autopsy). There were no characteristic symptoms of the disease and even roentgenologic findings were not particularly definite. The size varied from 1 to 7.5 centimeters. Surgical treatment of diverticula in the upper portion of the stomach is indicated when the presence of the diverticulum is proved and no other cause for the epigastric distress can be found. When present in the lower 2/3 of the stomach operative measures, preferably resection of the diverticula, are always advisable because of the possibility of an associated malignancy. An excellent bibliography is included in the paper.

J. Duffy Hancock, Louisville.

BAUER, WALTER.

*What Should a Patient With Arthritis Eat? Journal of the A. M. A., 104:1, Jan. 5, 1935.*

The author presents a useful classification of arthritis. He divides all arthritis into two main groups, one group the origin of which is known and a second group of unknown or uncertain origin.

In the group of arthritis of known origin, with the exception of gout, no special diet is indicated.

In the group of arthritis of uncertain or unknown etiology, the author distinguishes two groups which he states must be considered separately because they are distinctly different disease processes.

In the degenerative or hypertrophic arthritis, the etiology is the "wear and tear" incident to increased age and repeated trauma. Inflammatory processes, endocrine dysfunction and metabolic disturbances do not cause this type of arthritis. Other than a reduction type of diet in the obese to relieve a weight-bearing joint, no special diet is necessary.

Proliferative or rheumatoid arthritis is of unknown etiology. Infection is an important etiologic agent in the general opinion.

The omission of acid fruits and vegetables is one of diet used in treatment. These acid fruits are weak acids. They

are the chief source of Vitamin C. There appears to be no reason for removing these fruits from the diet.

There is no evidence to show that mixed diets—protein, fat, and carbohydrate taken together—are in any way incompatible.

There is no apparent truth in the theory of an "acid system" in rheumatoid arthritis. A well balanced diet maintains the acid-base balance of the body.

If food hypersensitivity exists it must be definitely determined and the offending food removed from the diet. If such hypersensitivity exists in rheumatoid arthritis, it must be rare.

A low protein diet in rheumatoid arthritis is not justified and may be harmful.

Reduced caloric intake has not been shown to be of value.

There has been no definite evidence to show that a low carbohydrate diet is of any special value in the treatment of this type of arthritis.

Because of the inadequacies of the average diet, the author feels that a high vitamin, high caloric diet with calcium, phosphorus and iron should be used in these cases.

Francis D. Murphy, M.D., Milwaukee.

LEONA M. BAYER, M.D., AND H. GRAY, M.D.

*Obesity Treatment by Diet, Thyroid and Dinitrophenol, Result of 106 Outpatients. Am. J. Med. Sc., Vol. 189, No. 1, p. 86, Jan., 1935.*

The authors summarize their results on the treatment of obesity under dietetic treatment supplemented with the administration of thyroid and dinitrophenol.

They advise a course of dietetic treatment before exhibiting dinitrophenol. They describe the ill effects of three cases who were treated with dinitrophenol.

Reports of the toxicity of this drug have persuaded many physicians to suspend its use altogether. There has been a number of fatal cases reported in the literature, and the drug unquestionably is being used by the laity as it is sold indiscriminately by the drug trade. The sale of dinitrophenol should be restricted to physicians' prescriptions, and in many instances physicians would do well to omit its exhibition in the treatment of obesity.

H. W. Soper, St. Louis, Mo.



## SECTION IV—*Roentgenology*

### Dysphagia—Roentgenologically Considered\*

By

L. S. OTELL, M.D.

and

FRED O. COE, M.D.

WASHINGTON, DISTRICT OF COLUMBIA

THE physician is consulted frequently by patients whose chief complaint is "difficulty in swallowing." A carefully taken history and a thorough physical examination may reveal the cause, may give some diagnostic clue or may be entirely misleading. In most instances the basic pathologic lesion is a matter of conjecture unless a more direct method of approach is employed.

The roentgen method not only gives valuable information concerning lesions both within and outside of the esophagus but involves no unpleasant manipulative procedures and is entirely without danger. The esophagoscope in the hands of the master is often an important adjunct in confirming the roentgen diagnosis and in many instances may give more accurate information concerning certain intraesophageal lesions. On the other hand it renders little assistance in the large group of extraesophageal conditions which may seriously interfere with swallowing. Concerning the bougie as a diagnostic implement in the esophagus we shall merely quote a passage from Barclay (1) in which he says: "Of the bougie it is difficult to write with patience. If other and less dangerous methods are available it is an act of crude barbarity to pass such an instrument for diagnostic purposes into a tube the walls of which may be the seat of simple or malignant ulceration or may be eroded by an aneurysm. The bougie is a most useful surgical instrument . . . but for diagnosis there is no other such savage relic in the whole of medicine or surgery."

The roentgenologist in his capacity as a consultant is intrusted with the oftentimes difficult problem of disclosing as far as possible the actual pathological condition which interferes with the swallowing act. He should therefore not only be thoroughly acquainted with the roentgen patterns of the various lesions which may be encountered but should be able to correlate them with the clinical manifestations. The history, the presence of other related symptoms, the laboratory findings and the physical examination are helpful in making a diagnosis and in the many doubtful cases which he encounters esophagoscopy should be advised.

There are many causes of dysphagia. The large group of diseases of the pharynx and larynx, *i.e.*,

acute tonsillitis, lingual tonsils, laryngeal and pharyngeal ulcerations are not of particular interest to the roentgenologist, inasmuch as these conditions are usually demonstrable by direct vision. The discussion in this paper will center around the large number of intraesophageal and extraesophageal lesions which for the sake of convenience have been divided into three groups depending upon their frequency of occurrence.

#### Group 1. (most common)

- a. Foreign bodies.
- b. Achalasia of the cardia (cardiospasm).
- c. New growths.
- d. Esophageal orifice hernia.

#### Group 2. (less common)

- a. Compression stenosis.
- b. Diverticula and pharyngeal pouches.
- c. Congenital atresia.
- d. Paralysis of the esophagus.
- e. Cicatricial stenosis (traumatic).
- f. Esophageal varices.
- g. Dysphagia of anemic women.

#### Group 3. (rare)

- a. Benign tumor.
- b. Peptic ulcer of the esophagus.
- c. Thoracic stomach.
- d. Syphilis.
- e. Tuberculosis.
- f. Esophagitis.
- g. Mycotic stenosis.
- h. Dysphagia associated with gastric lesions.
- i. Herpes, urticaria, angioneurotic edema, serum sickness.
- j. Spasm of the esophagus.
- k. Atony of the esophagus.
- l. Globus hystericus and hysteria.

#### FOREIGN BODIES

The diagnosis and ultimate behaviour of foreign bodies in the food passage is to a large extent a roentgenological problem. The roentgenologist usually comes in contact with these patients early and observes them either until the foreign body is removed or passes spontaneously.

The history and symptoms are important in the diagnosis. There is usually a subjective feeling that something is stuck in the throat. This may be fol-

\*From the Radiological Clinic of Drs. Groover, Christie and Merritt.  
Submitted January 7, 1935.



Fig. 1.

Fig. 1. Esophageal orifice hernia. A large portion of the greater curvature of the stomach lies above the diaphragm.

ful in showing the relationship between the esophagus and trachea. It should be remembered that flat opaque bodies always lie in the coronal plane when in the esophagus and in the sagittal plane when in the larynx. The most common location of foreign bodies in the esophagus is on a level with the clavicles. Opaque foreign bodies are usually easily demonstrable. Semi-opaque or non-opaque bodies offer much difficulty. In order to disclose the presence of a partially opaque or non-opaque body it is necessary often to rely on indirect evidence. The patient is given first a thin and then a thick barium mixture and its behavior is watched fluoroscopically and checked with roentgenograms. A foreign body may manifest itself by (1) a slight hesitation of the medium, (2) a forked stream such as is seen in benign tumors, (3) an actual filling defect, (4) a retention of the medium in a pocket about the foreign body, (5) spasm. Small balls of cotton wool impregnated with barium and swallowed without mastication may stick on the foreign body and disclose its presence and location. This procedure may interfere with the esophagoscopy examination if it should be necessary.

#### ACHALASIA OF THE CARDIA. (CARDIOSPASM)

Recent writers on this subject have been concerned with the choice of a name conformable with the newer knowledge regarding it and the pathology of the condition. The term "cardiospasm" has been virtually discarded. It has been demonstrated by the esophagoscope that the obstruction is not spasmodic. Moreover hypertrophy of the cardiac sphincter does not occur as would be expected were it due to spasm. The name "preventriculosis" has been used by Jackson (2), since, as he says it implies a location proximal to the stomach; an anatomical fact; it omits all implication as to etiology. Hurst (3) realizing the meaninglessness of the term "cardiospasm" asked Sir Cooper Perry to invent a name. He suggested the word "achalasia" which means absence of relaxation. The term has come into quite general use. The pathological findings are of particular interest. It was first suggested by Hurst (3) that possibly it was not a purely functional condition but was the result of organic change involving the neuro-muscular control of the sphincter. Rake (4) in 1925 was the first to demonstrate a round cell infiltration in Auerbach's plexus at the lower end of the esophagus. In a number of other cases degenerative changes resulting in more or less complete disappearance of the ganglion cells were found. These findings have since been confirmed by other investigators. The evidence is therefore quite convincing that achalasia is the result of organic changes in Auerbach's plexus. Mosher (5) feels that the primary factor is infection of the contiguous organs extending into the esophageal walls and producing fibrosis.

Dysphagia is the most prominent symptom but may not be recognized by the patient as such. He may be able to swallow but often does not realize that the swallowing act has not been completed. He may feel that food lodges in his throat. Other common findings are retrosternal fullness, regurgitation, and gaseous eructations.

lowed by odonophagia, dysphagia, aphasia or drooling at the mouth. The history may be misleading, particularly in children, and in all suspected cases a roentgen examination is advisable as a routine procedure. The presence of a foreign body in the esophagus is not ordinarily an indication for hurried action. Ulceration and perforation occur in many cases but a foreign body may remain in the esophagus for some time without causing complications. Foreign bodies with a sharp edge may perforate early unless removed. It is important to know how long the foreign body has been present but unfortunately the history is not always reliable.

Almost every conceivable object has been found in the esophagus. We observed one patient who had swallowed a package of safety razor blades which passed readily through the alimentary canal. Barclay (1) mentions a case in which a patient swallowed his week's wages, inconveniencing only the landlord who had to wait for his rent. Most foreign bodies which pass the esophagus will pass through the intestinal tract without difficulty if the patient is kept on his regular diet and bulky foods and cathartics are avoided. Objects most frequently lodged in the esophagus according to Jackson (2) are (1) bones, (2) coins, (3) safety pins, (4) artificial dentures, (5) buttons. In all of the instances in which bones, foods, coins, safety pins and buttons were found 95% of them were in the esophagus and the other 5% in the larynx and trachea. On the other hand 97% of the straight pins were found in the larynx or trachea.

*Roentgen examinations* in these cases should include everything from the nasopharynx to the ischial spines. Roentgenograms should be taken in various planes. Often a foreign body can be visualized only in the oblique position. Lateral views are particularly help-

The diagnosis cannot be made from the history but depends upon the roentgen and esophagoscopy findings. Both methods of examination are important and neither should be omitted.

The roentgen findings are quite characteristic. Preliminary examination of the chest may show a straight line shadow to the right of the heart and mediastinum. Fluoroscopic examination with an opaque meal shows the medium to float down the esophagus in parallel cords or as falling snow flakes. This appearance is due to the presence of fluid or food which has been retained in the esophagus. The medium stops above the cardia as a V-shaped constriction with smooth sharp outlines which come to a fine point. The esophagus above this point is usually dilated, sometimes to such an extent that it will hold large quantities of food and fluids. The walls are usually smooth and sharply defined but may show localized constrictions and bulgings due to peristaltic activity. The peristaltic waves may be reversed at times. In protracted cases the esophagus becomes elongated, in some instances as much as 10 centimeters. The lengthened esophagus bends on the diaphragm to the right and ventrally and may as a result produce a rounded instead of a V-shaped border at its lower end. The ultimate evacuation of the medium is interesting. It may be vomited; it may pass into the stomach in small spurts during the expiratory phase of respiration, or may be moved into the stomach in a whole column without any evidence of constriction at the cardia. Twenty-four hour retention in the esophagus is not uncommon.

### NEW GROWTHS OF THE ESOPHAGUS

There are many types of primary neoplasms of the esophagus but carcinoma is by far the most common. Carcinoma manifests itself in three forms; (1) epithelioma, which arises from the surface epithelium, is more frequent in the upper two thirds, is more prone to ulcerate, and has a tendency to perforate into the trachea, lungs, or mediastinum; (2) adenocarcinoma, which arises from the cells of misplaced gastric mucosa, is more frequent in the lower third, rarely ulcerates, and there is no tendency to perforate; (3) infiltrating type, in which the esophagus takes the form of a thick walled tube throughout its entire extent resembling linitis plastica and fibro-carcinoma of the stomach.

If the mortality of carcinoma of the esophagus is to be reduced below 100% early diagnosis is imperative

and recognition of the early symptoms is therefore essential. Jackson (6), after the study of a large number of cases, found the earliest symptoms to be vague and "neurotic" in character. The most frequently noted early symptoms were a slight queer feeling in swallowing, a feeling of nervousness before swallowing, vague sensations about the neck, a cramped feeling in the neck, a feeling that there is something wrong with the act of deglutition, or a sticking of food in the throat when eating rapidly. Dysphagia is always a late symptom and in some cases may not be present at all. The sudden onset of dysphagia in some instances is perplexing. The symptoms may date back only a few days or a few weeks and for this reason spasm may be suspected. It should be remembered that the sudden onset of dysphagia in carcinoma of the esophagus is not of uncommon occurrence. Pain is a very late symptom. It may not be so severe as in peptic ulcer or esophagitis and is found only in those cases where there is extensive ulceration

of the growth or an associated esophagitis.

Unfortunately the roentgenologist seldom sees this disease until it has run at least half of its course. In those cases where the early symptoms are suggestive and in which the routine roentgen examination shows no abnormality, the patient should be given some sort of irritant such as toasted bread crumbs or grated pineapple in order to bring on spasm which may be the only clue to the presence of a lesion. Esophagoscopy examination in these cases is



Fig. 2. Achalasia of the cardia. Note elongation and tortuous contour of the lower esophagus.

imperative. The roentgen appearance of the more advanced lesion is well known. As the patient swallows the opaque medium an abrupt hesitation is noted. It flows down to one side of the midline trickling over a ragged irregular defect. The outline of the growth may be detected in some cases. Dilatation of the esophagus above the lesion is usually not marked. Occasionally two defects may be noted in the esophagus or one in the esophagus and one in the stomach. Such double lesions are usually the result of extension through the lymphatics either from the esophagus to the stomach or from the stomach to the esophagus. Rarely do two primary lesions occur. Paralysis of the diaphragm is a late sign. Enlargement of the mediastinal glands in an adult is always an indication for thorough examination of the esophagus, inasmuch as a small neoplasm of the esophagus may cause extreme enlargement of these glands. Erosion of a malignant ulcer with per-



Fig. 3.

foration into the trachea is not uncommon. We have seen three such cases during the past year. It is always startling to see the lower bronchial trees fill with the barium mixture. Perforations are said to occur also as the result of abscess, syphilis and tuberculosis (Jackson) (6). Neoplasm may be confused with achalasia of the cardia (cardiospasm). Usually the age of the patient, the shorter history, and irregularity of the outline in neoplasm will differentiate the two.

#### ESOPHAGEAL ORIFICE HERNIA

Herniation of a portion of the greater curvature of the stomach through the diaphragmatic orifice is in general of two types which have not been clearly differentiated in recent roentgenological literature. In the first type the hernia may be as large as 10-12 centimeters in diameter; it is fixed and permanent; it is usually demonstrable in the upright position, and there is an associated congenital shortening of the esophagus. The second type is associated with the name of von Bergmann (7) who in 1932 clearly differentiated it from the first type. This variety of hernia is usually small, not more than 2-3 centimeters in diameter; it is not usually fixed but recurs when the patient assumes a horizontal or bending forward position; it is not demonstrable in the upright position, and to be visualized it is often necessary to increase the intra-abdominal pressure and examine the patient while drinking the opaque meal lying on the back. In this type, the esophagus is usually normal in length and a portion of the terminal esophagus may also herniate through the hiatus with the stomach.

An idea of the frequency with which esophageal orifice hernia occurs may be obtained by the experience of the authors. During the past few years they have seen as many of these hernias as all other esopha-

Fig. 3. Cicatricial stenosis of the esophagus resulting from the swallowing of lye. Note the large portion of the esophagus involved.

geal lesions combined. True it is, that they have looked for them in all examinations of the alimentary tract. Patients are observed both in the upright and horizontal positions both prone and supine at various angles and during deep and rapid respirations. Such measures are necessary in order to bring out the recurrent type. In many cases the hernia may be apparent for only a moment under the fluoroscope and may not be demonstrable at all on the roentgenogram.

In our experience this lesion has been found most commonly in middle aged or elderly women who are usually overweight and have considerable abdominal fat and a "eow horn" type of stomach.

The symptoms are often bizarre and may vary considerably in different cases. They may simulate those of duodenal ulcer or gall bladder disease. In other cases where the symptoms are more typical, esophageal hernia may be suspected. Several of our patients have been unable to assume a recumbent position without distress for several hours after eating a heavy meal. Some have found it necessary to take their evening meal a few hours earlier than usual in order to avoid retrosternal fullness and discomfort upon retiring. Dysphagia often is a prominent symptom particularly when the sack is large. The recurrent type may be suspected when pain or vague upper abdominal symptoms occur particularly at night or on bending over. The attacks in most cases are mainly nocturnal and disappear when the patient is up. Pain may occur just below the ensiform immediately after swallowing and in some cases may radiate to the arm and simulate angina. Occasionally the symptoms are so slight that they are elicited only on careful questioning. In some cases there are no symptoms and the discovery of the hernia is merely incidental to a thorough examination.

The roentgen appearance is characteristic in most cases. Before swallowing the opaque meal, a gas bubble may be noted in the hernial sac. As the meal is swallowed one notices first a slight delay at the cardia. Next, a compression defect appears on the concave side of the gastro-esophageal angle. At the same moment a pouch is visualized in this same area filling from below. The pouch is always situated just above the esophageal orifice and above the diaphragm. Many times when the pouch fails to fill completely, folds of gastric mucosa may be seen passing above the diaphragm through the hiatus. The recurrent type does not fill in the upright position. If this lesion is suspected it is advisable to observe the esophagus as the patient swallows the meal while lying on the back. Too drastic measures should not be used to increase the intraabdominal pressure. Filling the colon with gas and heavy compression may in themselves produce hernia and if complications are present, as is not unusual, serious damage may be done.

#### COMPRESSION STENOSIS

In the earlier stages of esophageal compression an organic lesion is often not suspected because of the vagueness of the symptoms. The roentgenologist is not consulted until the disease has run a protracted course.

Fig. 4. Barium in the right lower bronchus and inflammatory changes in the right lower lobe resulting from overflow from a paralyzed esophagus. The basic lesion was a chronic progressive bulbar palsy.

Roentgen examination of the chest will usually disclose the presence of an abnormal mass within or about the mediastinum. Examination of the esophagus with an opaque medium may reveal either a displacement or a filling defect depending upon the part of the esophagus involved normally. The esophagus is attached at both ends and sags somewhat in the midportion like a loose string. It can be readily seen that extreme pressure at or about the midportion will result primarily in displacement. Compression at one or the other points of attachment will produce a smoothly outlined defect simulating an intraesophageal mass. In those cases where displacement occurs the roentgen appearance can best be described by comparing it with that normally produced by the aortic arch. The esophageal shadow is decreased in circumference as the result of a smoothly outlined defect on the concave surface. The shadow of the compressing mass is often apparent and is in relation with the esophageal defect.

The most frequently encountered compressing lesions of the esophagus are as follows: (1) Aneurysm. Compression may result either from the saccular or dissecting types. The walls of the esophagus may become eroded and perforation may occur. (2) Abscess. Pyogenic or tuberculous retropharyngeal abscess may cause forward displacement of the trachea and esophagus and interfere considerably with the act of deglutition. A lateral view of the neck should always be a part of the roentgen examination in children who complain of dysphagia. We have been able to recognize retropharyngeal abscesses on several occasions before they have been discovered clinically. (3) Enlarged glands. Glandular enlargement causing esophageal compression may be the result of malignant lymphoma, leucemia, tuberculosis, syphilis, pyogenic infections or metastatic neoplasm. One should be particularly careful in such cases not to overlook a primary neoplasm of the esophagus. The widespread metastasis to the mediastinal glands in carcinoma of the esophagus may produce a pressure defect and may direct attention away from the primary growth. (4) Abnormalities of the great vessels. The dysphagia which may be the result of congenital displacement of the subclavian artery, transposition of the vessels or enlargement of the pulmonary conus incidental to a patent ductus arteriosus is known as "dysphagia lusoria." These are rather uncommon lesions and should be thought of in association with dysphagia of obscure origin. Extreme dilatation of the aorta may result in compression of the esophagus. (5) Cardiac enlargement. The extreme dilatation of the left auricle as seen in mitral stenosis often compresses the esophagus posteriorly or to the right to the extent of causing dysphagia. The authors recently observed a patient whose chief complaint was dysphagia incident to mitral stenosis. (6) Substernal thyroid. This condition should be differentiated particularly from benign intraesophageal tumor. These two conditions may not be distinguishable roentgenologically and esophagoscopy is necessary in doubtful cases. (7) Mediastinal and lung tumors. Any of the large group of malignant or benign tumors of the mediastinum or lung

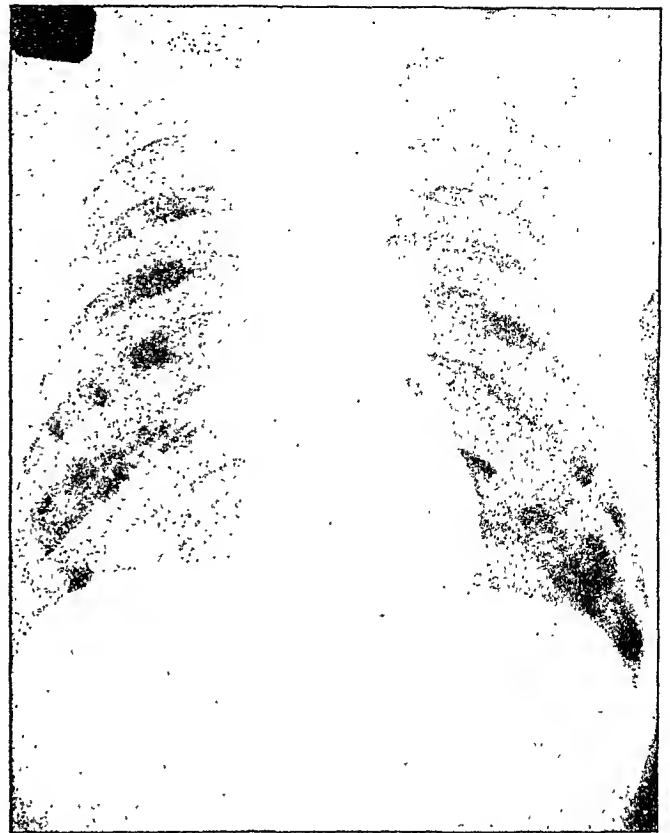


Fig. 4.

may compress the esophagus. (8) Spinal deformities. Extreme lordosis or bony productive lesions arising from the ventral surfaces of the vertebral bodies may compress the esophagus and cause dysphagia. (9) Enlargement of the left lobe of the liver. Primary or secondary tumor masses, abscesses or cysts of the left lobe of the liver may compress the lower esophagus. (10) Mediastinal or mesial effusions. In these lesions the esophagus may be compressed over a considerable extent of its length.

The differential diagnosis of these various compressing lesions of the esophagus is not within the scope of this paper.

#### ESOPHAGEAL DIVERTICULA AND PHARYNGEAL POUCHES

Diverticula of the esophagus rarely cause symptoms. They are usually small pouches attached to the esophagus by a thin neck and do not retain the barium for any length of time. The pulsion type arises from pressure from within the lumen and is usually associated with an esophageal stenosis below the opening. The so-called traction type is the result of localized pulling on the esophagus from adhesions. The esophagus must be already fixed in order for a diverticulum of this type to develop.

The pharyngeal type on the other hand may cause marked symptoms. There may be a sensation of incomplete swallowing, fullness in the neck and difficulty in emptying the pouch. Roentgen examination shows a semicircular sac with a smoothly outlined convex border below and a horizontal fluid level above. The medium flows over the top into the esophagus as the sac empties. In the smaller pouches, the opening into the esophagus can be seen to lie just ventral to the upper border of the sac.





Fig. 5.

### CONGENITAL ATRESIA

This condition, which is an endodermal developmental defect, is usually seen during the first few days of life. The inability of the infant to retain food, the complete regurgitation of the small amount taken, choking, coughing and cyanosis are characteristic findings and from these symptoms the diagnosis can often be made clinically.

Malformations of the esophagus are not particularly rare. We have seen three cases during the past year. The types of malformation vary from complete absence of the esophagus to a partial stenosis. The most frequently encountered types lie between these two extremes and take the form of a blind upper and lower pouch which do not communicate with each other, but either one or both of which may communicate with the trachea through a fistulous opening.

Roentgen examination is important for verifying the clinical impression, determining the site of obstruction, the degree of occlusion, and the presence or absence of communication with the trachea. In order to visualize the esophagus it is often necessary to insert a small rubber catheter and inject the barium slowly under fluoroscopic observation. The point of obstruction, which is usually just below the bifurcation of the trachea, appears as a rounded, smoothly outlined border with moderate dilatation above. If none of the medium is seen to trickle down beyond the constriction, the obstruction may be considered to be complete. The abdomen should be examined for the presence of gas in the intestines and stomach. If present it may be assumed that there is a communication between the trachea and the lower esophageal segment.

The mortality in cases of complete obstruction, either with or without communication with the trachea, is 100%. The child dies within a few days from aspira-

Fig. 5. Benign tumor of the esophagus. Note the forked stream.

tion pneumonia. The importance of recognizing the degree of occlusion and the relationship of the esophagus to the trachea cannot be over emphasized in view of a statement by Jackson (8) in which he says: "The yielding of congenital stenosis to peroral esophagoscopic treatment is quite usual in those cases in which there is no communication between the esophagus and the trachea or bronchus."

### PARALYSIS OF THE ESOPHAGUS

Paralysis of the esophagus is not a rare condition. We have seen several cases and many cases have been observed by others.

The muscles of the pharynx, soft palate, larynx, tongue or esophagus may be involved as a sequence to diphtheria, cranial nerve neuritis, bulbar lesions or myasthenia gravis. Recently we had occasion to observe the esophagus in a case of myasthenia gravis and found that the medium behaved much the same as in other neuromuscular anomalies. One of our associates, Christie (9), has recently reported a case due to chronic progressive bulbar palsy and has pointed out the fact that the roentgenologist is often in a position to direct attention toward the possibility of a neuromuscular lesion. Other bulbar conditions which may result in dysphagia are syphilis, hemorrhage, and the bulbar type of poliomyelitis. Brahdy and Lenarsky (10) have recently reported a large series of acute poliomyelitis in which dysphagia was often a distressing symptom. In most cases relief occurred within a week. This is, they point out, to a great extent consistent with the course of bulbar lesions in general. The majority of them either progress rapidly to cause death or improve in a short time.

Roentgen examination in these cases discloses a complete stoppage of the meal in the posterior pharynx and the first portion of the esophagus without definite evidence of constriction. The medium is waltzed about in the posterior pharynx and overflows into the pyriform sinuses and often into the larynx and may fill the lower bronchial tree as in one of our cases. It may be washed down by drinks of water but still clings to the pharyngeal recesses and to the walls of the upper third of the esophagus. If it reaches the lower two-thirds of the esophagus it seems to pass through readily. This is interesting in view of the dual nerve supply to the esophagus. The upper third, which contains striated muscle, is nerved by the ninth and eleventh nerves through the nucleus ambiguus, whereas the non-striated muscle fibers of the lower two-thirds are nerved by the tenth nerve through its dorsal nucleus.

Relaxation of the laryngeal musculature may result in symptoms of dysphagia and give the same roentgen appearance as esophageal paralysis. This condition was first described by Quinke (11) and was called "laryngeal ptosis."

### CICATRICAL STENOSIS (TRAUMATIC)

The swallowing of corrosive poisons such as household lye and cleansers is by far the most common cause of scar tissue constriction of the esophagus. Such accidents occur most commonly in children.

Progressive dysphagia is the most prominent symptom. It may not develop for months or even years



Fig. 6. Syphilis of the stomach resulting in back pressure dilatation of the esophagus.

after the initial injury. Periods of almost complete inability to swallow may alternate with periods when there is no difficulty. Such symptoms are often misleading, and may result in an erroneous diagnosis unless careful attention is directed to the history. Occasionally corrosives may pass through the esophagus without injury to this organ but may cause a pyloric stenosis.

The lower and middle portions of the esophagus are most often involved and from one to two-thirds of the tube may be stenosed. This is accounted for by the fact that when the corrosive is swallowed the cardiac orifice closes reflexly and the column of liquid remains in the esophagus for a short time.

The roentgen examination is a valuable aid in disclosing the presence of the lesion, its location and extent and differentiation particularly from carcinoma. The esophagus above the stenosis is usually widened and sausage shaped. The medium trickles down from the most dependent portion in the midline as a very fine needle like stream. The strictured portion is usually of the same diameter throughout but occasionally one or more localized dilatations may be observed. In those instances where the stenosis occurs in the upper third the appearance may simulate that of a diverticulum. In the latter condition however, the stream is seen to overflow to one side whereas in stenosis it passes downward from the most dependent portion of the globular shadow. Carcinoma may cause some confusion, but is usually distinguishable by the jagged, irregular appearance of the outline. The roentgen appearance of benign strictures is fairly characteristic but the differentiation of the various types cannot be made from the roentgen appearance alone.

#### ESOPHAGEAL VARICES

The first case of esophageal varices in which the roentgen characteristics were described was that of Wolf (12) in 1928. Since then two cases have been reported by Hjelm (13), two by Beutel (14), five by Schatzki (15), and one by Kirklin and Moersch (16). At a recent meeting of the American Roentgen Ray Society, Holmes and Schatzki reported a large series of cases. We have had occasion to observe one case.

Dysphagia is rarely a prominent symptom. Attention is first directed to the alimentary tract because of hematemesis. Gastric ulcer or cancer is usually suspected clinically.

The varices are best demonstrated by using a thick barium mixture. They appear as semicircular defects interspersed with lace like areas of increased density, the latter representing the medium in the crevices between the veins. The roentgen appearance may simulate that of carcinoma but closely resembles that of multiple polyps. The presence of cirrhosis of the liver is confirmatory evidence of the nature of the lesion.

#### THE DYSPHAGIA OF ANEMIC WOMEN

##### *(Plummer-Vinson Syndrome)*

This condition which has sometimes been referred to as the Plummer-Vinson (17) syndrome, was, first described by Kelly (18) and Paterson (19) but without details as to the type of anemia present. In recent years this syndrome has become well recognized particularly in England. Hurst (3) has seen a consider-

608

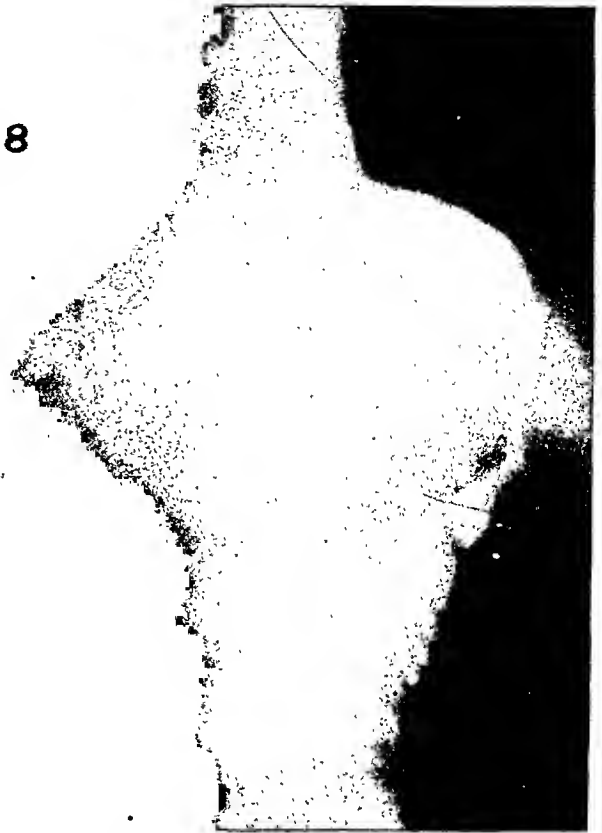


Fig. 6.

able number of cases and papers have been written on the subject by Pyle (20), Jones (21) and Owen, Suzman (22) and others.

The syndrome occurs most commonly in middle aged women and is characterized by anemia, glossitis and dysphagia. The anemia is usually of the hypochromic microcytic type and is rarely primary. Achlorhydria or hypochlorhydria may be present. Atrophic glossitis is a constant finding and is similar in all respects to that found in the primary anemias. The glossitis may extend to the mucous membrane of the pharynx and first portion of the esophagus. Plummer and Vinson (17) considered the dysphagia as an hysterical manifestation but Hurst (3) feels that it is due to incoordination of the muscles which initiate deglutition consequent to a disturbance in the neuro-muscular mechanism. The pharyngo-esophageal sphincter which is normally closed does not relax after the food has been propelled into the pharynx by the tongue, thus resulting in retention of food in the posterior pharynx.

Roentgen study of these cases shows no abnormality of the esophagus. There may be a slight delay of the meal in the posterior pharynx.

#### BENIGN TUMORS

Moore (23) has made the statement that benign tumors are pathological curiosities. The reports particularly in the roentgen literature would so indicate.

Glandular retention cysts are found occasionally at autopsy but produce no symptoms and are not demonstrable on roentgen examination. Polyps are the most common benign tumors of any practical importance. They may be single or multiple and are usually attached by pedicles to the anterior wall of the esophagus behind the cricoid cartilage. Sometimes a polyp may be forced up into the mouth during the act of

vomiting and may be bitten off by the patient. Several such instances have been recorded. Spontaneous evulsion of other types of benign tumor occurs. Fibromata, lipomata, hemangiomata and myomata have been found in the esophagus. Pape and Spitznagel (24) have reported two interesting cases of myoma of the esophagus. In one the tumor, which was 5 cm. in diameter was situated in the first portion of the esophagus and was mistaken for a substernal thyroid. In the other the tumors were multiple and were situated in the lower esophagus, some of them projecting on pedicles into the stomach.

Benign tumors may produce marked dysphagia with typical signs of stenosis.

The roentgen findings depend to a large extent upon the type and size of the tumor. Small polyps which are attached by a pedicle may not be demonstrable. Large tumors show a characteristic forked stream with a defect in the center as the medium passes down either side of the tumor. A tangential view may disclose a semilunar, smoothly outlined defect. Non-opaque foreign bodies produce similar appearances, as do also extraesophageal lesions which are in contact with the esophagus at its attached ends. Esophagoscopy is necessary in such cases in order to arrive at a correct diagnosis.

### PEPTIC ULCER OF THE ESOPHAGUS

The apparent rarity of peptic ulcer of the esophagus in the roentgen literature is perhaps due to the fact that the lesion is seldom recognized. Jackson (25) in 1929 reported having seen twenty-one active ulcers and the scars of sixty-seven healed ulcers in 4,000 endoscopic examinations. Friedenwald, Feldman and Zinn (26) have been able to recognize thirteen cases in their practice. Other investigators have recorded smaller numbers and many single cases have been reported.

A description of the symptoms in most of the cases agrees quite closely. Although dysphagia is not often noticeable the patient becomes afraid to eat because of pain and regurgitation. The pain and discomfort usually appear beneath the sternum during the taking of solid foods and occasionally a half hour or more after meals. Alkalis usually give relief. Hematemesis is a frequent complication and may be fatal. Perforation into the mediastinum, pericardium or peritoneum is the usual cause of death.

The ulcer is usually single. It is situated on the posterior wall in the lower third of the esophagus just above the cardiac sphincter. It varies in size from a few millimeters to ten centimeters in diameter. It has all of the macroscopic and microscopic characteristics of chronic ulcer of the stomach or duodenum.

The most constant roentgen manifestation in the cases reported has been spasm. This was true of several of Jackson's cases and its importance as a diagnostic sign has been particularly stressed by Barclay (1). Friedenwald and Feldman (26) are the only authors who have succeeded in visualizing the crater of an esophageal ulcer roentgenographically. These same authors have described four types of defect in the ulcerated esophagus: (1) mucosal erosions, which are not as a rule demonstrable roentgenographically but may show spastic phenomena or a "fleck"; (2) niche or penetrating, which resembles the niche of a penetrating gastric ulcer; (3) spastic defects; (4) per-

forating, which is rarely observed roentgenographically because of the extreme illness of the patient.

### THORACIC STOMACH

This uncommon congenital defect is often associated with inability to take food in satisfactory amounts. True dysphagia is not a prominent symptom.

Roentgen examination shows the presence of a short esophagus proportionate to the high position of the stomach. The esophagus does not pass through the diaphragm and the stomach is always above the diaphragm. The duodenum usually passes through the diaphragmatic hiatus occupying the normal position of the esophagus. These features serve to distinguish this condition from the more common herniation of the stomach through the diaphragm.

### SYPHILIS

Guyot (27), in 1931, collected from the literature fifty-seven cases including two of his own of tertiary syphilitic lesions of the esophagus. Eleven of these were confirmed at autopsy. Fifteen others were recognized endoscopically and were said to have been cured by specific therapy. Thus less than half of the cases reported have been proven to be syphilitic.

We have had no personal experience with this condition. All suspected syphilitic lesions of the esophagus which have come under our observation have eventually been proven to be carcinoma.

Progressively developing dysphagia is usually the chief complaint. In the more active stages the symptoms may simulate those of peptic ulcer of the esophagus or non-specific esophagitis. As the ulcer heals, the lumen gradually becomes narrow and constricted and at this time dysphagia may be quite marked.

There is no characteristic roentgen pattern in syphilitic esophagitis. The presence of a gumma cannot be detected either by roentgenograms or the esophagoscope. In the diffuse type with stenosis the defect may simulate that of a new growth or if more extensive may be identical with cicatricial stenosis. The diagnosis cannot be made from the roentgen findings alone. The history, esophagoscopy, serological examination and the therapeutic test are all necessary in arriving at a diagnosis.

### TUBERCULOSIS

Tuberculosis of the esophagus is practically never observed by the roentgenologist because it occurs usually in the terminal stages of pulmonary tuberculosis. Small mucosal erosions may occur as the result of swallowing tuberculous organisms, but the ulcers rarely assume the characteristics which they do in the lower ileum and cecum. Areas of ulceration may result from extension from bronchial lymphnodes, the trachea, the dorsal vertebrae or even the lungs. Roentgenologically these ulcers cannot be distinguished from non-tuberculous ulcers.

It should be remembered that the dysphagia which is a common symptom in advanced pulmonary tuberculosis is usually the result of ulceration of the epiglottis.

### ESOPHAGITIS

Acute esophagitis is frequently the result of trauma from the swallowing of corrosives, but may occur also in blood stream infections even to the point of ulceration. Acute inflammation of the esophagus is not uncommon in pneumonia.

Chronic esophagitis according to Mosher (5) is a fairly common condition. It heals by depositing fibrous tissue and consequently is capable of producing stenosis. This same author has shown convincing evidence that cirrhosis of the liver and infection of the gall bladder are the chief predisposing causes of infection of the esophagus. He states further that fibrosis of isolated areas is fairly common particularly associated with arteriosclerosis. Jackson (2) feels that the most common cause of chronic esophagitis is stasis of food and secretions incidental to a stenosing lesion. He mentions strong alcoholic beverages, mustards, pepper and hot foods, hasty gluttonous eating and poor mastication as contributing causes. He has noted the frequent appearance of chronic esophagitis in all stenosing lesions of the esophagus, particularly marked in achalasia of the cardia.

Dysphagia is not a prominent symptom in chronic esophagitis unless there is some stenosis. The most common complaint is a vague dull ache behind the sternum which may radiate to the back.

The roentgen appearance in acute esophagitis shows no variation from the normal. As a rule roentgen and esophagoscopy examinations are contraindicated in the acute stage. Chronic esophagitis cannot be recognized roentgenologically as such and can only be surmised as a possible factor in stenosing lesions.

#### MYCOTIC STENOSIS

Actinomyces and blastomycosis of the esophagus deserve only passing attention because of their extreme rarity. The roentgenologist may not see a single case in a life time and then only after stenosis has occurred.

The roentgen appearance does not differ from other stenosing lesions and the diagnosis can be made only by bacteriological examination.

#### DYSPHAGIA ASSOCIATED WITH GASTRIC LESIONS

Back pressure dilatation of the esophagus with relaxation and incompetency of the cardiac sphincter may result from (1) hour glass contraction of the stomach from the scar of an old peptic ulcer, (2) linitis plastica or fibro-carcinoma of the stomach with marked narrowing of the lumen, (3) operative intervention when there has been an extensive resection of the stomach. The swallowing of a large amount of air has been observed in one of our cases as a cause of dysphagia. The patient in question gave a history which was suggestive of a new growth. Roentgenologically the esophagus showed nothing abnormal. The patient swallowed such large quantities of air that the stomach became extremely dilated, and symptoms of dysphagia ensued.

#### HERPES, URTICARIA, ANGIONEUROTIC EDEMA, SERUM SICKNESS

These uncommon diseases have been described and included under one heading by Jackson (28). The lesions are quite similar in all and manifest the same characteristics in the mucous membrane of the esophagus as in the mucosa of other parts of the body and on the skin.

The diagnosis can be made only with the esophagoscope. Nothing abnormal can be noted either fluoroscopically or on the roentgenograms. The authors have had occasion to examine roentgenologically two patients who had urticaria of the skin and mucous

membrane and complained of difficulty in swallowing. In neither was there any demonstrable abnormality of the esophagus. The lesions in the esophagus are usually associated with lesions elsewhere on the body and these findings together with the esophagoscopy appearance are conclusive.

#### SPASM OF THE ESOPHAGUS

Esophageal spasm is usually the result of ulceration of the mucosa or the presence of a foreign body, but may occur without any demonstrable lesion as in a case reported by Grier (30).

The history may be of assistance in differentiating an organic from an idiopathic spasm. In the organic type the degree of spasm may vary with the same type of food or may actually disappear from time to time, whereas in the idiopathic type the spasm is usually more marked and persistent.

Spasm may take the form of (a) a B-shaped incisure, as is frequently seen in peptic ulcers of the stomach; (b) a concentric constriction as is seen in prepyloric gastric spasm; (c) a V-shaped narrowing.

The presence of esophageal spasm is always an indication for esophagoscopy study.

#### ATONY OF THE ESOPHAGUS

This entity has not received much attention in the roentgen literature. It was described first by Von Rosenheim (28) and the X-ray characteristics have been established by Holzknecht (29) and Olberta. It is a functional disturbance of the musculature of the esophagus which may cause mild or severe dysphagia.

During the act of swallowing, fluoroscopic examination reveals the medium clinging to the walls of the esophagus throughout its entire length where it remains for some time before going into the stomach. There is no evidence of stenosis. The roentgen appearance differs from that of esophageal paralysis in that in the latter there is regurgitation into the posterior pharynx and the medium clings to the walls only in the upper third rather than throughout the entire length.

Atony of the esophagus is found particularly in people with a neuropathic constitution.

#### GLOBUS HYSTERICUS AND HYSTERIA

Many patients who complain of dysphagia are told by a physician that their trouble is the result of "nerves," and this without more direct methods of examination. Such a conclusion is usually not only erroneous but dangerous. It is true that dysphagia which may be purely functional is not uncommon in neurotic patients but it should be remembered that there is no reason why a neurotic individual may not have an organic lesion in the esophagus. We believe that all patients who complain of dysphagia should have roentgen or esophagoscopy examinations or both unless the reason for the dysphagia is otherwise apparent.

Dysphagia as a manifestation of hysteria is extremely rare. Globus hystericus which is probably not a definite entity is more common.

Nothing abnormal is noted roentgenologically in these functional conditions. Barclay (1) believes that there is a definite causal relationship between calcification of the thyroid cartilage and globus hystericus. Such calcifications are seen so commonly without symptoms that it seems more probable that the association is merely a coincidence.

## REFERENCES

1. Barclay, A. E.: The digestive tract. Cambridge University Press, 1933.
2. Joekson, C., and Jackson, C. L.: The Cyclopaedia of Medicine, Vol. 5, F. A. Davis Co., 1932.
3. Hurst, A. F.: Some disorders of the esophagus. *J. A. M. A.*, 102:582-587, February 24, 1934.
4. Rake, G. W.: *Guy's Hosp. Rep.*, 76:145, April, 1926, 77:141-150, April, 1927.
5. Mosher, H. P.: Involvement of the esophagus in acute and chronic infections. *Arch. of Otolaryng.*, 18:563-598, November, 1933.
6. Joekson, C.: Carcinoma and sarcoma of the esophagus: plea for early diagnosis. *Am. J. M. Sc.*, 169:625, May, 1925.
7. von Bergman, G., and Goldner, M.: Funktionelle Pathologie. Berlin, Julius Springer, 1932, p. 68.
8. Joekson, C., and Jackson, C. L.: Pulmonary symptoms due to esophageal disease. *Arch. of Otolaryng.*, 18:731-745, December, 1933.
9. Christie, A. C.: The roentgen findings in chronic progressive bulbous polyp. *Am. Jour. of Roentgen. and Rad. Ther.*, 27:5, May, 1932.
10. Brahdly, M. B., and Lenarsky, M.: Difficulty in swallowing in acute epidemic poliomyelitis. *J. A. M. A.*, 103:229-234, July 28, 1934.
11. Quinke, H.: Laryngoptose. *Berlin kl. W.*, 49, 1908.
12. Wolf, G.: Die Erkennung von Oesophagus-Varizen im Röntgen-bilde. *Fortschr. o. d. Geb. d. Röntgenstrahlen*, 37:890-893, 1928.
13. Hjelm, R.: *Acta Radiologica*, 12:146-151, 1931.
14. Beutel, A.: Esophageal varices, *Acta Radiologica*, 13: Fase. 5:527-532, 1932.
15. Schatzki, R.: Die roentgen-diagnose der oesophagus-und mognenvarizen und ihre Bedeutung für die Klinik. *Fortschr. a. d. Geb. d. Roentgenstrahlen*, 44:28-29, July, 1931.
16. Kirklin, B. R., and Moersch, H. J.: Report of a case of roentgenologically demonstrable varices complicating splenomegaly. *Radiology*, 17:573, 575, September, 1931.
17. Vinson, P. P.: *Minnesota Med.*, 5:107, February, 1922.
18. Kelly, A. B.: Spasm at entrance to oesophagus. *J. Laryng. Rhin. and Otol.*, 34:285, August, 1919.
19. Paterson, D. R.: Clinical type of dysphagia. *J. Laryng. Rhin. and Otol.*, 34:289, August, 1919.
20. Ryle, J. A.: Case of oesophageal spasm with severe anemia (Plummer-Vinson Syndrome). *Guy's Hosp. Rep.*, 77:33-34, January, 1927.
21. Jones, A. M., and Owen, R. D.: Dysphagia associated with anemia. *Brit. Med. J.*, 1:256-257, February 18, 1928.
22. Suzman, M. M.: Syndrome of anemia, glossitis and dysphagia. *Arch. Int. Med.*, 51:1-21, January, 1933.
23. Moore, A. B.: Benign lesions in cordiae portions of esophagus and stomach: roentgenologic diagnosis. *J. A. M. A.*, 94:12-15, January 4, 1930.
24. Pope, R., and Splitznagel, K.: Über Oesophagusmyome. *Forsch. a. d. Geb. d. Röntgenstrahlen*, 44:616-625, November, 1931.
25. Joekson, C.: Peptic ulcer of the esophagus. *J. A. M. A.*, 92:369, February 2, 1929.
26. Friedenwald, J.; Feldman, M., and Zinn, W. F.: Tr. Am. Gastro-enterol. A., 31:93, 1929.
27. Guyot, R.: La syphilis de l'oesophagie en portieolar ou point de vue anatomopathologique. *Ann. d'otolaryng.*, 505:526, May, 1931.
28. Rosenheim, Th.: Über Spasmus und Atonie der Speiseröhre. *Deut. M. W.*, 45:740, 1899.
29. Holzknecht und Olbert: Die Atonie des Oesophagus. *Zschr. f. klin. M.*, 92, 1910.
30. Grier, G. W.: Spasm in middle of oesophagus. *Radiology*, 2:265, April, 1924.

## ABSTRACTS

BOLES, RUSSEL S., AND GERSHON-COHEN, JACOB.

*Intestinal Tuberculosis: Pathologic and Roentgenologic Observations. J. A. M. A.*, 103:1814, Dec. 15, 1934.

In a series of 1000 consecutive autopsies, tuberculosis of the lungs was found in 226 cases. In these 226 cases of active and healed pulmonary tuberculosis an ulcerative type of intestinal lesion occurred in sixty-three cases. Primary hyperplastic tuberculosis of the large bowel was not observed in these 1000 autopsies.

A study of the relationship of the type of pulmonary lesion to intestinal ulceration shows the highest incidence in the fibro-ulcerative cavernous type of pulmonary disease. It may also occur in cases of early or exudative pulmonary tuberculosis. It occurred more frequently in women of the Negro race between 20 and 40 years of age. No cases of ulcerative tuberculosis were found in chronic fibroid or miliary tuberculosis.

The double contrast enema is recommended as an important aid in the diagnosis of ileocecal tuberculosis. It is claimed that this diagnostic aid will make early recognition possible and therapy may be instituted early.

Francis D. Murphy, Milwaukee, Wis.

KANTOR, JOHN L.

*Regional (Terminal) Ileitis: Its Roentgen Diagnosis. J. A. M. A.*, 103:2016, Dec. 29, 1934.

The author reports the roentgenological findings in six proven cases of the regional or terminal ileitis.

In the roentgen diagnosis of this condition the standard opaque meal is used. Observations are made hourly from

the period just before the cecum is filled to the normal period of ileae emptying.

Abnormalities are found in the colon and ileum.

In the colon the changes are due to reflex spasm. This spasm may involve the entire colon but more characteristically, the cecum alone. These changes are not constant. Actual involvement of the colon by adhesions or fistulae may occur. In such a condition a fixed deformity results.

In the ileum occur the most important changes. These consist of a constant defect in the filling of the terminal ileum; proximal to the filling defect the ileum showed an irregular shape or a peculiar taper point. Obstruction occurred in the small intestine proximal to the filling defect in two cases. The most striking finding is a thin, slightly irregular linear shadow extending from the region of the last visualized loop through the entire extent of the filling defect and ending at the ileocecal valve. This so called "string sign" represents the attenuated barium filling of the greatly contracted intestinal lumen.

In the differential diagnosis the appendix shadow must not be confused. Spastic segments of small intestine may be differentiated because of their wider lumen, denser shadow, smoother outline and variation in the location of the loops in subsequent exposures.

The "string sign" of regional ileitis remains constant even for days.

Tuberculoma, stenosing sarcoma and syphilis of the terminal ileum must also be considered in the differential diagnosis.

Francis D. Murphy, M.D., Milwaukee.

## SECTION VIII—Editorial

The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Association is in no way responsible for editorial expressions.

### THE CONCEPT OF "COMBINED ACIDITY" IN GASTRIC JUICE STUDIES

IN a recent article by Lay Martin (1) concerning the significance of the combined acidity of gastric juice, the Author concluded: "It seems wise to abandon the common conception of the expression 'combined acidity' since, in the first place, it is erroneous as it is applied, and, in the second place, open-minded recognition of the buffer strength of gastric juice between pH 4.0 and 8.0 may lead to further investigations of significance." For many years, clinicians and investigators concerned with the problems of gastric chemistry have measured both free and combined acidities. Conclusions concerning gastric secretory activity and its correlation with other physiological or pathological phenomena have, for the most part, been based on the value for "free HCl," or on that for "total acidity." Interpretations of the "combined acidity" value found in the literature consist simply of a statement of random variations in the amount of soluble protein present.

This lack of interest in "combined acidity" derives from several sources. In the first place, the values are generally small as compared with the experimental errors involved in their determination, and consequently their quantitative reliability is open to question. Secondly, the physiological significance of such values—particularly as this bears on problems of clinical importance—is still an open question. As Michaelis pointed out some time ago (2), the combined acidity value is influenced by the concentration not only of soluble protein, but also of phosphate and lactate ions, and the source of these constituents of the gastric juice has not as yet been clearly defined. Finally, our knowledge concerning buffer curves and the importance of pH in contradistinction to titration acidity is a relatively recent product of modern physical chemistry.

Now, abandonment of the older conception of "combined acidity" is, to my mind, highly desirable, not only because the idea is chemically indefinite, but because of its sterility as a physiological concept. There can be no doubt that the buffer substances contained in ordinary gastric juice, the presence of which result in this "combined acidity," are physiologically of great importance. As I have shown in my own studies of gastric secretion in dogs, the pure parietal secretion—uncontaminated by other secretions or foreign substances—contains practically no buffer salts (3). On the other hand, the admixture of mucus or other alkaline secretion from the gastric mucosa with this HCl-containing fluid will result in the presence of such

"combined acidity." In fact, there probably exists a statistically definable quantitative relation between the magnitude of the "combined acidity," the relative amount of these alkaline secretions, and the reduction in acidity which results from their presence.

Having demonstrated that fluctuations in gastric acidity result from a variation in the amount of these buffer-containing secretions, rather than from a variation in the HCl concentration of the parietal fluid itself, it follows that some adequate quantitative measure of the buffer substances in gastric juice is of importance both clinically and experimentally. In consequence of his own work with gastro-globulin and other protein-like constituents of gastric juice, Dr. Martin proposes that we substitute for the combined acidity, as it is determined at present, the exact titration value between pH 4.0 and pH 8.0; *i.e.*, to end-points which are determined by comparison with standard buffer solutions. This would certainly constitute a well-defined measure of the buffering power of the gastric juice in this pH interval. In my own work (4), I have employed a similar procedure, though the pH interval chosen was slightly different, the range extending from 3.5 to 7.0. On the other hand, Michaelis recommended pH 2.8 as the lower limit of this range and Shohl and King (5) employed 3.0. Any one of these procedures will yield a well-defined measure of the total buffer content of gastric juice, and as such they are all worthy of consideration. Furthermore, they require no physico-chemical technique beyond the capacity of the ordinary clinical technician, although they do demand somewhat greater care in their performance than that usually given a gastric titration. It must be remembered, of course, that such a determination of gross buffering power will not tell us anything about the distribution and characteristics of the various buffer substances present. This information can be derived only from a complete titration curve over an even more extensive pH range. Although the time and labor required for the determination of a buffer curve are so great as to prohibit the utilization of this method for routine clinical work, these should be no drawback for experimental purposes, nor should the technical demands on training and equipment constitute a hindrance in any modern physiological laboratory. The fruit of such effort will more than justify the labor.

In conclusion, it seems to me that some official recognition should be taken of Dr. Martin's recommendation regarding the abandonment of the classical notation of "combined acidity." As for a substitute procedure which "may lead to further investigations of significance," any decision in this regard should come from a body designated to consider the matter from its various aspects, clinical as well as experimental. Such a group, acting under the authority of the American Gastro-enterological Association, might consult very extensively with individual workers throughout the country. A report of the varied opin-

"For a splendid review of present day information as to the toxicity of vitamin D, the reader should turn to an article on the Physiology of the Sterols, including Vitamin D by Charles E. Bills in *Physiological Reviews*, 15 (1):1-98, 1935."

1. Lay Martin: *Amer. Jour. Diges. Dis. and Nutrit.*, 1:330, 1934.
2. Michaelis, L.: *Harvey Lectures*, 22:59, 1926-27.
3. Hollander, F.: *J. Biol. Chem.*, 97:585, 1932; 104:33, 1934; *Amer. Jour. Diges. Dis. and Nutrit.*, 1:319, 1934.
4. Hollander, F.: *J. Biol. Chem.*, 91:481, 1931.
5. Shohl, A. T., and King, J. H.: *Bull. Johns Hopkins Hosp.*, 31:158, 1920.



ions so obtained would, at the very least, stimulate further thought on the matter, and might possibly furnish a new and well thought-out procedure to replace the present one for determining "combined acidity."

Franklin Hollander, New York, N. Y.

## IS THE PUBLIC BEING STAMPEDED IN REGARD TO VITAMINS?

**T**HE other day I saw a woman with indigestion and a nervous breakdown. The story was puzzling until the husband explained, feelingly, that at each mealtime his wife wrangled with the children over the eating of spinach and carrots and the taking of cod liver oil until everyone at the table was exhausted and in a bad humor. Was this necessary? Will the children of this fairly well-to-do, middle-class American family come to grief if the mother stops stuffing them? I think the chances are that they will not.

*How did people "get by" before vitamins were discovered?*

Certainly when I was a child my mother knew nothing of vitamins, they had not yet been discovered; and yet today I stand six feet in my stockings, and my legs are straight. How did I and millions like me grow strong and well in the old days? Simply because we had a varied diet and enough of it. We had fresh food; most of us in this country had milk and butter and eggs and fruit, and we did not need cod liver oil because we spent much of our childhood out of doors in the sun.

While I do not wish to minimize the value of modern dietetic research and its splendid discoveries, I still feel that we are passing through a stage of experimentation in which vitamins are being forced on children and adults without sufficient thought and understanding. The historically minded man cannot help remembering that every substance ever found useful in the prevention or cure of disease once had to go through a stage during which it was given for everything. In each instance enthusiasm slowly waned, and eventually, the more enlightened type of physician saw clearly when and when not to use the substance. In many cases, it turned out that the drug should never have been used at all.

*Is enough as good or better than a feast?*

Certainly most of us will be better satisfied about the use of vitamins when research workers are able to tell us how much of what is learned from experiments on rats is applicable to man, and particularly to adult man. Already we know that the rat does not react to the lack of vitamins in all respects as man does; he can make at least one of them himself somewhere in his body. Perhaps this explains the fact that a research worker, who, a few years ago, found the diet of Mexican children in our Southwest decidedly insufficient, according to standards based on experience with rats, had to admit that the children seemed to be about as large and as healthy as their better fed playmates whose parents came from the North. Incidentally, individual men react differently to lack of vitamins. As every polar explorer knows, in the old days some men promptly succumbed to scurvy while a few seemed to be almost immune.

We physicians also want to know how much of the several vitamins must children and adults get every day to remain in health? We are only now beginning

to get a little information in regard to this, and some people are beginning to see that what is needed by the child may not be needed at all by the adult. We want to know, also, if it does any good to keep stuffing a child with vitamins after it has enough. May not enough be as good as a feast? Recently, I saw a woman with indigestion and a number of curious symptoms produced apparently by the taking of a quart of orange juice a day. Unfortunately, the pyorrhea, which her dentist had hoped to cure with an overdose of vitamin C, was still present.

It may well be that there is a number of diseases that can be cured with the help of large doses of some one vitamin, but I cannot help looking with a little scepticism on some of the enthusiastic papers that are now being published. Usually the work is not done so that one can be sure that vitamins alone produced the improvement noted in the patient; and, again, the historian reminds us that the easiest road to the front page of scientific magazines has always been through the reporting of startling cures obtained with a new and popular therapeutic agent. As I said before, when the excitement quiets down, it is found, sometimes, that the germs that the new drug was supposed to kill thrive on it, and physicians must wonder then how certain papers came to be written.

*Vitamin D in large doses is a poison*

We know that large doses of vitamin D will kill an animal in a short time, and we know that smaller doses injure the arteries. Under these circumstances, it is well that several research workers are trying to fix the upper limit of safe dosage. Fortunately, evidence is accumulating to show that the injurious dose is so much greater than the useful one that under ordinary circumstances no one need worry.\* But, unfortunately, today circumstances are not ordinary, and we may have to fear two tendencies: one, that of people to go to extremes, and the other, that of present day manufacturers of foods to add too much vitamin D to their products. Today the desire of purveyors of food and popular drugs to advertise that their product is full of vitamins is so strong that they may go too far and something may have to be done to restrain them.

Let us imagine a child who, to begin with, does not need extra amounts of vitamin D because he is out in the sun all day. He is getting all he needs in his food, and his bones are growing straight and strong. But his well-intentioned mother is forcing on him large doses of the very powerful, irradiated ergosterol; he is getting more "D" in his pint or more of irradiated milk; the cows which supply the milk are being fed yeast and other substances to increase the vitamin content of the cream and butter; the baker is adding "D" to his bread, and, as I write, manufacturers of breakfast foods and chewing gum, and even cough drops, are all hastening to join in the race.

Personally I rather resent having to take unasked-for vitamin D every day simply because the men who supply me with food want a new selling point. I see the advantages of supplying extra vitamins to the children of the poor, but when I, an adult, decide to stuff myself with such a powerful drug as vitamin D, I would rather have some control over the process, and I would rather get my supply from the drug store.

\*For a good review of some of the literature, see Reed, C. I., Symptoms of Viosterol Overdosage in Human Subjects. *Jour. Am. Med. Assoc.*, 102:1745-1748, May 26, 1931.



If present practices keep up, I fear that before long the government will have to step in and say that vitamin D may be added, let us say, to milk and/or bread, but not to other foods. I understand that the owners of the irradiation patents are worried over the situation and are refusing huge sums offered for new licenses. But this will not prevent manufacturers from adding vitamin D in other ways.

Fortunately, as yet, none of the other vitamins seem to be hurtful when given in large doses.

#### *When vitamins are needed*

The worried housewife should be taught that vitamins are so largely concerned with growth that they are most important to the pregnant woman, the nursing mother, and the growing child. In adult life, and when there is no extra stress, such as that of pregnancy, lactation, or prolonged illness, they are less important, and there seems to be little reason for forcing them on people who are already living on a liberal and well-chosen diet.

Although I would not think of denying the safety value to growing children of milk, eggs, fresh fruit, green vegetables, and cod liver oil, I think we should sometimes remind worried mothers that some of the healthiest, huskiest, fattest children, with the most perfect teeth, are to be found among the uncivilized Eskimos who never saw a cow, a hen, a fruit, or a vegetable. Living almost entirely on meat and fish, they get their vitamins by eating much of the food raw, and particularly by eating the inner organs, such as liver, kidneys, and marrow.

I would like to show a group of these healthy Eskimos to every enthusiast who insists that the only way to health is through eating spinach, or wholewheat, or orange juice. I would like him to see that there is no one indispensable or perfect "Nature food." He should learn that the defect in one food can easily be compensated by the special richness of another. For instance, white flour is certainly deficient in vitamins; but the baker adds so much milk and yeast, and now vitamin D, and the eater of the bread spreads so much butter on his slice, that it is silly to worry about the loss, during the milling; of the little wheat germ and its contained vitamins.

If we, in this country, were living on bread alone, the government might well pass a law making wholewheat compulsory for all bread making, but in view of the fact that our children can so easily get, and are getting, their vitamins from foods other than wheat, anyone who would advocate such a law would only expose his ignorance of the science of nutrition.

#### *The thoughtlessness of forcing growth stimulators on the girl babies of overly-large parents*

One thought that does not seem to occur to people is this: if several of the vitamins are primarily stimulators of growth, are physicians and intelligent, well-read, and conscientious mothers, really using their brains when they force large doses of these substances on the already oversized children of oversized parents? Such stuffing with vitamins may be all right for the girl babies of people who are short in stature, but is it not rather thoughtless when the father is six feet four and the mother five feet ten?

Already many of our boys in this country are too tall for comfort in the standard chair, bed, theater seat, or Pullman berth. As I travel about the country I am impressed with the number of girls I see who

are so tall or so big in every way that they are embarrassed and unhappy, and their chances of marrying are diminished. During the last century, every generation in this country has tended to be a little taller than the preceding one; it would seem that a reasonable limit has been reached, and I doubt if we really want to go on producing huge men and, particularly huge women.

#### *Does the giving of vitamins prevent colds?*

One of the sales' arguments for giving vitamin A has been that it will prevent colds or make such infection milder. Although some experiments on animals and children suggested that this might be true, two reports of controlled studies on two groups of persons, one given extra amounts of vitamins and the other not, now show that these substances cannot be counted on to influence respiratory infections.

#### *Disease due to avitaminosis is probably rare in American adults*

The medical profession would probably do well to point out to the worried dietitians and mothers of families that disease which can be definitely ascribed to avitaminosis is very rarely seen among American adults of the middle or upper classes. Even the physician with a very large practice will see only a few cases a year in which he will suspect that the symptoms are due to too great a narrowing of a diet. Usually, such a patient is old: he may be a recluse who cooks for himself, or a psychopathic food crank who is fussy about eating and is full of prejudices, or he may be a red-nosed bum who has been trying to live on whiskey. Not infrequently the victim is a patient with peptic ulcer or ulcerative colitis who has been living too long on milk and little else.

It is interesting also to note that evidence is accumulating to show that, at times, and perhaps particularly in the case of non-tropical sprue and pernicious anemia, a disease due to the lack of certain substances in the food may be brought on by the failure of the intestine to absorb properly. At times, disease may appear only when to avitaminosis there is added another factor such as infection. This is thought to be the case in beriberi.

#### *It is not necessary to give rough foods in order to supply vitamins*

Advertisements in the magazines and the propaganda of food faddists have given many laymen the idea that the foods rich in roughage and vitamins are the most digestible and health-giving. This view must be combatted, and at times it must be pointed out to people that, especially when they are suffering with indigestion, they can easily obtain desired vitamins without eating a lot of indigestible cellulose-containing food. They can now buy vitamins in a concentrated form at the drug store.

#### *The dangers of sensitizing infants and children*

Sometimes I wonder if the present tendency to feed infants with foods formerly reserved for children and adults is having anything to do with what seems to be a tremendous increase in the incidence of hay fever and other disorders of allergic origin. There are reasons for believing that the intestinal mucous membrane of the infant is more permeable to foreign protein than is that of the adult. If this be true, we are probably sensitizing many children who in the old days of

breast feeding or milk formulas would never have suffered with allergic troubles. Doubtless this is only one cause of the increase in allergic diseases, because it seems probable that with the cultivation of enormous areas of the land, there has gone a big increase in the growth and distribution of those weeds whose pollen is so hurtful.

Certainly many of the sufferers from allergic disease seen today were born before the era of spinach and orange juice, but if it should appear later that part of the increase in the incidence of allergic disease is due to the sensitization of infants and children by too early stuffing with foreign protein, then we will have to avoid this; and if in that future day we still desire to give overdoses of vitamins, then, at least in the case of the children of allergic parents, we will have to give the vitamins and salts in pure form as is now done in the case of dietetic research with rats.

Unfortunately, as yet, it has not occurred to many people that one does not have to sensitize a child to orange juice in order to give him a milligram of ascorbic acid, nor does one have to stuff him with eggs or spinach in order to supply a little iron. Incidentally, Rohmar, Bezsonoff and Sanders now claim that an infant up to the age of fourteen months can make his own vitamin C.

A great artist was once asked with what he mixed his paints. "With brains, Sir," was the answer. Let us more often mix our prescriptions with brains: with real thought of exactly what we do and do not want to accomplish in the individual case.

#### Summary

Those persons who are now stuffing themselves or others with vitamins are not always well informed or logical in their behavior. As always happens with new therapeutic agents, vitamins are now being used to cure many diseases. As yet one cannot tell how much of the information obtained with rats should be applied directly to human beings, and especially to adults.

Vitamins are largely stimulators of growth and hence they are of value mainly to the growing child, the pregnant woman, and the nursing mother.

Information is still needed as to the adequate dose of the various vitamins for children and for adults. It is important to know whether or not it helps to stuff more vitamins after enough have been given. Since vitamin D is a lethal poison, we should know exactly the upper limit of safe dosage. It looks now as if the addition of vitamin D to foods will soon be overdone. If every purveyor of foods adds it to his product some children may get too much.

Those enthusiasts who get too excited about the necessity for forcing particular foods, such as orange juice or whole wheat, should keep in mind the uncivilized Eskimo with his perfect teeth, his chubby children, and his diet of fish and seals.

It is suggested that it may be undesirable to stuff girl babies of oversize parents with powerful stimulators of growth. Already many American girls are too tall for comfort.

Recent clinical trials have cast much doubt on the assumption that the giving of vitamin A will prevent colds.

Results of a careful questionnaire indicate that the leaders of American medicine rarely see disease due definitely to avitaminosis in middle class or even poor adult men and women.

It should be pointed out to laymen that one does not have to eat rough and indigestible foods to get vitamins and mineral salts. The daily ration of these substances can now be bought in the drug store in the form of a pill.

The question is asked if an apparently great increase in the incidence of allergic disease may not be due in part to the present-day practice of stuffing infants with foods for the handling of which their delicate intestinal mucosa is not yet ready.

Walter C. Alvarez, Rochester, Minnesota.

#### DR. SIBRAND LUPS' MONOGRAPH CONCERNING "CHRONIC ULCERATIVE COLITIS" AND AN APPRECIATION OF ITS TRANSLATION INTO ENGLISH BY DR. ABEL J. BAKER

TO all of our readers, undoubtedly, will come profit and pleasure from the printing of Dr. Sisbrand Lups' original studies concerning the bacteriologic factor in the etiology of "chronic ulcerative colitis."

The research has been conducted in a masterly and unbiased fashion; the data are presented excellently; illustrations and tabulations vividly tell their own stories. Moreover, this Journal's publication of Dr. Lups' studies is the first appearance of the work in the English language—a printing copyrighted by the Author.

While to Dr. Lups' and his European publishers our grateful thanks are given for permission first to reprint the work in English and to use the original copper plates for the beautiful illustrations, our major indebtedness goes to the translator, Dr. Abel J. Baker, Grand Rapids, Michigan.

When Dr. Lups' monograph and its accompanying illustrations reached us, an immediate—and for a time—puzzling-problem presented, namely that of adequate translation by a *trained, capable internist*. "Translation hacks," commonly laymen, easily are located, but such translations as they return lack those very necessary scientific values to words and phrases which only can be given by a physician and scientist. Even on the faculties or staffs of our most widely known schools of medicine, clinics or hospitals, it was not possible to uncover the person whom we felt the task demanded: an internist of standing who also was scientifically solid and who, though an American, read (and could think in) "Holland Dutch" as a language twin to his American.

In this quandary, happily the Editor recalled the capabilities of a former class-mate, Dr. Baker. Not a little time was consumed overcoming Dr. Baker's well-known modesty and claims as to his inability to bring to the task of translation a full degree of scientific adequacy. We were sure of his ability; our chief concern was that one so thoroughly occupied in professional consultations never could spare the time needed for so formidable a job. Eventually, all arrangements were made and the translation submitted. How thoroughly and faithfully Dr. Baker has performed his task, the printed article demonstrates far more eloquently than could any words of ours.

Finally, just the degree of indebtedness which our readers and the management of the Journal owe Dr. Baker perhaps can be appreciated when we set forth here that not alone did the Translator devote many valuable hours to the work but that, personally, he bore every penny's expense concerned with sten-

graphers, typists and the multitude of "incidentals" which pile up during a task of this nature!

Formal thanks, of course, have been transmitted to Dr. Baker. Such seem to carry scant weight compared with the work performed—the sacrifices of needed rest, recreation, other reading, even the financial burden. Whatever may be the individual tributes which readers "on their own" may transmit to Dr. Baker is their concern and responsibility. However, we at the Editorial Office acknowledge most gratefully that the Translator removed from our shoulders a heavy editorial burden and from our "counting house" (and from those of several presumably dollar-strong institutions to whom ineffectually we turned for financial aid for this particular piece of work) a load which in these times could not be sustained.

Further Dr. Baker has given American medical literature a contribution which not alone most eminently is worth while but he has allowed physicians and scientists of these Western lands a glimpse of what investigative efforts are being carried on by such well grounded, careful students and clinicians as are connected with the institutions of Holland: a land whose medical men and scientific literature, alas, we know but too vaguely—not alone because few of us read Dutch, but because Hollanders frequently seek their scientific audiences in German and French journals. Thus, they are apt to lose their national identity and that of their most admirably managed and equipped scientific institutions.

Frank Smithies.

## NOTICE

THE 38th Annual Session of the American Gastroenterological Association will be held under the Presidency of Dr. B. B. Vincent Lyon, Philadelphia, at Hotel Traymore, Atlantic City, New Jersey, on Monday and Tuesday, June 10th and 11th.

Not only has the Association prepared an unusually strong program for the coming meeting, but inasmuch as its session will be held immediately prior to the opening of the combined meeting of the American and the Canadian Medical Associations (the first of such gatherings) attendance at this annual meeting of the American Gastroenterological Association offers extraordinary opportunities to enjoy and to benefit from the co-ordinated social and scientific presentations of these great national organizations.

In an early issue, this Journal will print the complete program of the Association's sessions. Members of the Association who plan to attend this week of unusual scientific and clinical value would be wise if *immediately* they reserved hotel space. Indications are that "last minute" reservations will lead to disappointment. Already numerous prominent hotels are booked solid.

*Write the hotel of your choice at once.*

Russell S. Boles, Secretary,  
American Gastroenterological Association,  
Rittenhouse Plaza,  
Philadelphia, Pa.

## SECTION IX—*Book Reviews*

*(This section is open to contributions from any medical reader, whether a member of the Editorial Council or not).*

The Physiology of the Gallbladder by A. C. Ivy. Physiological Reviews, 14:1-102 (Jan.) 1934.

THIS comprehensive publication summarizes the present status of our knowledge of the physiology of the gallbladder.

The gallbladder manifests the principal general activities of the intestine, namely, absorption, secretion, and motor activity. Absorption, which is selective, consists chiefly in the abstraction of water and certain inorganic salts. The secretion is mucoid in character and its enzymatic content is insignificant. Motor activity is of the same general type found in the intestine, that is, propulsive and non-propulsive. The biliary ducts have secretory but little absorptive activity, and they may or may not manifest motility, depending on the species.

Absorption of water and inorganic ions by the gallbladder is accomplished according to the law that the gallbladder content tends to remain isosmotic with serum, as determined by the freezing point method. Experimental evidence indicates that the maximal rate at which water is absorbed by the gallbladder is about 6 c.c. per hour, leading to a concentration in animals and man of six to ten times the hepatic bile that enters the gallbladder. Concentrating ability, however, is limited and no greater concentration is found in forty-

eight than in sixteen to twenty-four hours. The wall of the gallbladder also absorbs sodium, chloride, and bicarbonate ions, with an increase in acidity of the bile as it becomes concentrated. It is of interest to note that anatomic evidence indicates only blood capillary tufts are present in the mucosal folds of the gallbladder, and consequently substances absorbed by the epithelium pass primarily into the vascular and not into the lymphatic system.

Evidence indicates that calcium is absorbed by the normal gallbladder; calcification of the wall of the gallbladder has been produced experimentally; and an injured gallbladder mucosa has excreted fluid containing calcium. Bile pigments are apparently not absorbed in appreciable quantities. Ivy concludes that the available evidence indicates that small quantities of bile salts may be absorbed by the normal gallbladder and that inflammation or irritation of the gallbladder increases the rate of absorption of bile salts. Evidence on the absorption of cholesterol is difficult to evaluate, but the data indicate that normal gallbladder mucosa absorbs relatively small amounts, if any, of cholesterol daily, and that the inflamed mucosa, because of its cholesterol content, may add cholesterol to the contents of the gallbladder by desquamation. The pathologic significance of this latter process certainly is open to further investigation. There is no evidence that bile fat passes through normal mucosa

of the gallbladder during the concentration of bile.

The effect of drugs and nerve influences on absorption of the gallbladder is indicated by the fact that stimulation of the vagus, peripherally, increases the rate of concentration, whereas stimulation of the splanchnic nerves decreases the rate of concentration. Atropine does not prevent normal absorption or normal concentration. Absorption of tetradiophenolphthalein from the gallbladder probably occurs at a slow rate. Evidence indicates that in cases of acute cholecystitis, concentrating ability is lost, as it is also in empyema, hydrops and secondary contraction of the gallbladder; in the papillomatous gallbladder with hypertrophied rugae, however, it is increased.

**Secretion.** Under normal conditions it may be said that the gallbladder forms only a small quantity of mucoid secretion, and that under conditions of acute irritation it ceases concentrating and pours out a fluid, which teliologically may be compared to a type of catharsis.

**Motor activity.** Two types of motor activity are manifested by the gallbladder: (1) tonic contraction, which produces a sustained rise in pressure within the gallbladder, persisting for from five to thirty minutes or more, and (2) tonus rhythm, which is manifested by rhythmic contraction and relaxation, occurring at a rate of two to six times a minute.

**Innervation of the gallbladder.** Ivy and Schragar found that pain, vomiting, and respiratory disturbance result from distention of the gallbladder. Pain was abolished by splanchnic section, chiefly on the right; nausea and vomiting were abolished by section of vagus fibers, and respiratory disturbances were reduced by section of either the splanchnic or vagus nerves. In regard to motor innervation, evidence still indicates that although the vagus and splanchnic nerves carry motor and inhibitory fibers, the vagus nerve is preponderantly motor and the splanchnic nerve inhibitory for the gallbladder.

**Evacuation of the gallbladder.** Ivy believes that three types of evidence unequivocally demonstrate that evacuation of the gallbladder occurs in man by way of the cystic duct, namely, surgical evidence, chemical analysis of duodenal contents, and roentgenologic evidence. Fats and fatty acids are the most active evacants, and proteins (meat) rank next; carbohydrates, on the other hand, are comparatively ineffective in causing evacuation of the gallbladder. According to Boyden, the lecithin fraction of egg-yolk is the most potent fraction, but pure lecithin is not so efficacious as crude. Liquid petrolatum does not evacuate the gallbladder.

Ivy states that he has failed to find in the literature a completely negative report of the effect on the gallbladder of magnesium sulphate insofar as "evacuation of the gallbladder is concerned, that is, a report in which a fairly large series of normal subjects was used and in which some evidence of evacuation was not obtained for some of the subjects studied. The story is different, however, in regard to therapeutic and diagnostic efficacy." The mechanism of action of magnesium sulphate still is not clear. The effect is apparently not produced by a humoral route and, although the theory of a reciprocal reflex mechanism is favored, insufficient evidence is available to answer the question satisfactorily. The consensus of opinion is that magnesium sulphate is not so effective as is egg-yolk or cream, or as olive oil and oleic acid.

Ivy points out that while a number of writers have referred to the hyperkinetic, vagotonic, sthenic, or hyperactive gallbladder, and to the hypokinetic, sympathotonic, asthenic, or sluggish gallbladder or to various types of gallbladder response, the evidence presented is not yet conclusive. There is, apparently, an intermittency in gallbladder evacuation in man. Boyden has referred to phases of contraction which follow a fairly definite sequence, and he has described three types of response of the gallbladder of man to stimuli. These consist of: (1) an initial relaxation of the gallbladder, with apparent simultaneous closure of the sphincter, (2) rapid evacuation due to contraction of the gallbladder and probably to relaxation of the sphincter, and (3) a sluggish type in which the initial phase of emptying is followed by filling and in which the time of evacuation is prolonged. His studies also indicate that in fifty normal persons the time of evacuation ranged from sixteen minutes to four and one-half hours; some observers, however, believe that it may be longer.

Mechanisms that have been suggested for excitation of the gallbladder include: (1) local stimulation by distention or "pungent" bile, (2) nervous reflex excitation from various parts of the gastro-intestinal tract, (3) reflex excitation from spinal cord and higher centers, and (4) humoral agents. The only possible interpretation of the evidence at hand is that a hormone mechanism is concerned in contraction and evacuation of the gallbladder, the hormone (cholecystokinin) being closely related to, but not identical with secretion. The problem of the rôle of duodenal motility and the sphincter of Oddi in evacuation of bile is still not settled. As Ivy states, although the gallbladder may evacuate without the assistance of the duodenum or sphincter of Oddi, one cannot avoid the fact that there exists an important choledochoduodenal mechanism for regulating the flow of bile into and out of the gallbladder. That duodenal motility and tone play a part in controlling the flow of bile into the duodenum is accepted as a fact by all observers. Evidence may also be interpreted to indicate that in those species with a gallbladder, the common duct possesses a special sphincteric mechanism which is intimately coordinated with duodenal tone and peristalsis but which may also function independently. It may be regarded as established that the sphincter of the choledochoduodenal mechanism is essential for the filling of the gallbladder. "In the relatively rapid type of evacuation of the gallbladder of man and dog which occurs after the ingestion of a meal of egg-yolk and cream or fat, the evidence shows that the chief factor concerned is a rise in intra-gallbladder pressure. This rise is due primarily to a more or less sustained tonic contraction of musculature. The contraction is excited in part by a hormone (cholecystokinin) and by reflex nervous mechanisms (cephalic or gastro-intestinal). The sphincter of Oddi and the duodenal musculature promote evacuation by relaxing and permitting bile to be expelled by the contracting gallbladder. The evidence shows that a reciprocal functional relationship exists between the gallbladder and the choledochoduodenal mechanism, but whether this relationship is reciprocally causal is an open question. The evidence also shows that duodenal peristalses are not essential for but assist evacuation."

In summarizing the evidence of the relation of disease of the biliary tract and gastric acidity, Ivy

states that it can only be said that there is a tendency in man toward anacidity which is not specific in character and has no appreciable significance in the diagnosis and symptoms of the affliction.

In summarizing the evidence on the rôle of the gallbladder in the function of biliary tract and digestion, Ivy states that the gallbladder serves as a "factor of safety" in digestion and in regulating the pressure in the biliary passages. In fact, there are indications that the pressure-regulating function of the gallbladder is more important than its function of storage of bile for digestive purposes. Ivy also believes that a search should be made for functions of the gallbladder other than those which have been enumerated already.

Dwight L. Wilbur, Rochester, Minn.

*The Automatic Diseases or the Rheumatic Syndrome*, by T. M. Rivers, M.D., Dorrance & Co., Philadelphia, 1934, pp. 299, \$3.00.

THIS book contains a scholarly account of the autonomic nervous system together with a consideration of a variety of diseased states which are believed to be dependent, more or less directly, on abnormalities of this system. The author is a fellow of the American Medical Association residing in Kissimmee, Florida. Between 1923 and 1930 he published three or four papers dealing with the treatment of abrasions, contusions, and fractures. Since 1930 five articles have appeared from his pen in the "Journal of the Florida Medical Association." The titles of these suggest that they represent the basis of the present monograph. The author in his preface states that living in a small community and working in general practice he found his clinical material scarce; but instead of letting this hamper his efforts he tried to make it work to his advantage by giving more attention to the study of his cases. In conjunction with his clinical observations he attempted some laboratory work. Basing his efforts on the study of Barger of Edinburgh and others who had already determined that

the toxins of local infection were amines, he spent his spare time testing the action of various amines on membranes and joints of turtles, frogs, and guinea pigs, and learned that amines as well as other agents "sometimes pass their morbid action through the cranio-sacral nerves."

The book is interestingly written and the subject matter is well arranged. A number of misconceptions and erroneous statements of fact appear—for instance, that the distribution of lime salts in the body seems to be governed by vitamins A and D, and that products of metabolism, as creatin and creatinin, pass their augmentory action through the thoraco-lumbar nerves to produce hypertension and the diseases related to hypertension, and that an excess of carbon dioxide in the tissues causes the formation of excess uric acid, and that gout is due to excess of uric acid in the blood, and that painters develop gout from lead inhaled from their paints, and that vitamin D serves little if any purpose in the body development without the ultraviolet ray, and that death in most cases of angina pectoris results from intense spasm of the aorta, and that resection of parts of the colon is the most dependable treatment for epilepsy. On the whole, however, the broad conception that much disease of the rheumatic category depends on amines, acting principally on fibrous tissue by way of the cranio-sacral nerves, will deserve serious consideration if it ever comes to be proved that cranio-sacral nerve fibers pass into the muscles or the skin or the joints.

It is apparent from the 135 journal articles and 32 monographs named in the bibliography of his book that the author has read widely in this field. He has an inquisitive mind and the ability to correlate facts which to many would seem to defy correlation. That he is a very wise and skillful physician is indicated by the perusal of the chapter on heart affections. The delightful flights of speculative fantasy into which the subject of this book leads him are tempered throughout by a large measure of critical judgment.

R. M. Wilder, M.D., Rochester, Minn.

## SECTION XI—Societies, Programs and Proceedings

### PRELIMINARY PROGRAM OF THE THIRTY-EIGHTH ANNUAL MEETING OF THE American Gastro-Enterological Association

To be held at

ATLANTIC CITY

MONDAY AND TUESDAY, JUNE 10 AND 11, 1935

HEADQUARTERS AND ALL SESSIONS AT  
HOTEL TRAYMORE

MONDAY, JUNE 10, 1935

MORNING SESSION, 9:00 A. M.

Memorial Address of Dr. Albert Bernheim

Dr. David Riesman

Presidential Address

Dr. B. B. Vincent Lyon

1. "Studies on Crystalline Vitamin B<sub>1</sub>—Observations in Diabetes."

Dr. Martin G. Vorhaus, New York, N. Y.

Dr. R. R. Williams (by invitation),

New York, N. Y.

2. "Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes."  
Dr. T. L. Althausen,  
San Francisco, California.  
B. Blomquist, M.A. (by invitation)  
San Francisco, California.
  3. "Gastro-intestinal Manifestations of Hyperinsulinism."  
Dr. Seale Harris, Birmingham, Alabama
  4. "Present Conceptions of Calcium Metabolism."  
David L. Thomson, M.D. (by invitation)  
Associate Professor of Biochemistry,  
McGill University, Montreal, Canada.
- 11:30 A. M.
5. THE ALVAREZ LECTURE  
Founded in 1929 by Dr. Frank Smithies  
Lewellys F. Barker, M.D.  
Professor Emeritus of Medicine, Johns Hopkins University, School of Medicine,  
Baltimore, Md.  
Adjournment for Luncheon 12:30 P. M.  
to 1:30 P. M.  
2 P. M.
  6. "Abdominal Pain as a Misleading Symptom of Spinal Cord Lesions."  
Dr. Everett D. Kiefer, Boston, Mass.
  7. "Experimental Studies of Chronic Visceral Infection in Relation to Gastro-Enterological Problems."  
Dr. Martin E. Rehfuess, Philadelphia, Pa.  
Dr. Guy N. Nelson (by invitation),  
Philadelphia, Pa.
  8. "The Present Status of Colon Bacillus Vaccine Therapy."  
Dr. John G. Mateer, Detroit, Michigan.  
Dr. James I. Baltz, Dr. James Fitzgerald,  
and Dr. Harris L. Woodburne,  
(by invitation)
  9. "Serum Lipase: Its Diagnostic Value."  
Dr. M. W. Comfort, Rochester, Minn.
  10. "Report of Enzyme Committee."  
Dr. A. H. Aaron, Chairman, Buffalo, N. Y.
- EXECUTIVE SESSION
- (Associate members are requested not to attend)
- Annual Dinner, 7:30 P. M.  
Hotel Traymore, Atlantic City, N. J.
- Guests of Honor  
Dean Lewis, M.D.,  
Professor of Surgery, Johns Hopkins University, Baltimore, Md.  
L. J. Austin, F.R.C.S.,  
Professor of Surgery, Queen's University,  
Kingston, Ontario.
- TUESDAY, JUNE 11, 1935  
MORNING SESSION, 9:15 A. M.
11. "Traumas Resulting From Sigmoid Manipulations."  
Dr. Burrill B. Crohn, New York, N. Y.  
Dr. Bernard D. Rosenak (by invitation),  
New York, N. Y.
  12. "The Cause of Faulty Digestion After Removal of the Stomach."  
Dr. Edward S. Emery, Jr., Boston, Mass.
  13. "Experimental Studies in Gastric Physiology in Man. III. The Motor Function of the Operated Stomach."  
Dr. Harry Shay, Philadelphia, Pa.
  14. "Observations on Ulcerations Adjacent to Experimental Gastric Pouches in Dogs—A Preliminary Communication."  
Dr. Asher Winkelstein, New York, N. Y.
  15. "Gastrosocopy with a Flexible Gastroscope."  
Rudolf Schindler, M.D.,  
Visiting Professor of Medicine, University of Chicago, Chicago, Ill.
  16. "Gastric Syphilis."  
Dr. Clement R. Jones, Pittsburgh, Pa.  
Adjournment for Luncheon, 12:30 P. M.  
to 1:30 P. M.  
1:30 P. M.
  17. "Effect of Drugs on the Isolated Colon of Man."  
Dr. J. A. Barga, Rochester, Minn.
  18. "Psychogenic Factors in Ulcerative Colitis."  
Dr. Albert J. Sullivan, New Haven, Conn.
  19. "Obesity and its Treatment."  
Walter R. Campbell, M.D., University of Toronto, Toronto, Canada.
  20. "Experiences with Postoperative Jejunal Ulcer and Gastrojejunal Fistula."  
Dr. Frank H. Lahey, Boston, Mass.
- To Be Read By Title
1. "Absorption from the Pathologic Colon."  
Donovan C. Browne,  
New Orleans, La.
  2. "Rationale of the Treatment of Bleeding Ulcer—A Clinical and Experimental Study."  
Benjamin M. Bernstein,  
Brooklyn, New York.
  3. "The Levulose Tolerance Test."  
Stockton Kimball and Roger S. Hubbard,  
Buffalo, New York.
  4. "The Effects of Repeated Injections of Histamine on Gastric Secretion."  
Leon Schiff,  
Cincinnati, Ohio.
  5. "Gastrosocopy with the Semi-flexible Gastroscope."  
Wm. A. Swalm and Chevalier L. Jackson,  
Philadelphia, Pa.
  6. "Personality Study in Cardio-spasm: The Meaning of the Disorder from the Standpoint of Behavior."  
Edward Weiss,  
Philadelphia, Pa.
  7. "The Absorption of Unaltered Protein from the Normal and the Abnormal Gastro-intestinal Tract."  
Irving Gray, Mathew Walzer,  
(by invitation),  
Brooklyn, New York.
- (The Medical Profession is Cordially Invited)



## SECTION XII—"The Clinic"

### Traumatic Duodenal Ulcer in a 10 Year Old Boy

By

JACK WITHERSPOON, M.D.  
NASHVILLE, TENNESSEE

**D**UODENAL ulcer due to external violence is looked on with skepticism but has long been recognized. Numerous cases, proven by autopsy, operation, X-ray and clinical history, are to be found in medical and medico-legal literature.

Chronic peptic ulcer may occur at any age. It is quite uncommon in children.



Fig. 1. "Pine Tree" Deformity Duodenal Ulcer in a Child.

#### CASE REPORT

We desire to present such a case in a 10 year old white boy, oldest of four children. He complained of cramping pains in the abdomen and under the ensiform cartilage, nausea, loss of appetite, loss of blood from the bowel, and loss of weight. In the latter part of September, 1934, six weeks before we saw him, he was playing during recess in the school yard. He was tripped, and fell on his abdomen, knocking the breath out of him. He was carried into the school house where he lay in the rest room for a while, then he was sent home. He did not vomit, but that night complained of nausea and pain in the

abdomen. His father, a school teacher, stayed up all night with him, rubbing his abdomen and applying hot packs to it. The next morning the patient passed blood from the bowel and for the next few weeks nearly every stool was black or contained blood. He developed anorexia and indigestion. A few hours after eating, cramping and burning occurred, followed by food relief. He frequently vomited and on several occasions vomited blood. The pain was not continuous, but when it occurred the little boy placed his hands on his stomach, and bent over and cried. Sodawater frequently induced vomiting, but usually gave relief. In six weeks he had lost about 12 pounds in weight. Prior to the passage of a bloody stool he was often weak, nauseated, and his temperature sometimes rose as high as 102°. He became quite weak, remained away from school for two weeks and on the bed most of the time.

His previous medical history is not important. He has had measles and chicken pox. He has not had tonsillitis nor any continued fever. There was no lack of C vitamin in his diet. Early last Summer, while visiting his grandmother, he ate a good many June apples and developed stomach ache and diarrhea. He was seen by a doctor who kept him in bed a few days until he recovered. There were a few recurrences of enteritis but he regained his weight and was in good health when school started.

Examination showed a thin, anemic, debilitated little boy, with a temperature of 100°, and pulse of a 100. His skin was dry and pallid. His throat, chest, heart, lungs and extremities were not noteworthy. A few superficial lymph glands were palpable. The abdomen was flat, the spleen and liver were not enlarged. There was tenderness in the epigastrium near the mid line below the ensiform cartilage. No mass could be felt. The area of tenderness was protected by marked rigidity of the recti muscles. Pressure caused nausea. There was no tenderness or rigidity about McBurney's point. The sigmoid

flexure of the colon could be felt and rolled but caused no pain. His urine showed a trace of albumin. Blood examination showed Hemoglobin 50%, red cells 3,500,000, and leucocytes 13,000. He had been sick in bed a week, and had vomited blood, and passed black stools.

Fluoroscopically the barium meal entered his stomach without delay. The



Fig. 2. Penetrating Juvenile Duodenal Ulcer with Spastic Pyloric Ring.

stomach was high and hypertonic. The pylorus was spastic. No filling defect or deformity was seen in the stomach. The stomach was filled. The first portion of the duodenum presented a constant filling irregularity similar to that seen in a duodenal ulcer in an adult. The deformity was close to the pyloric ring, and there was lagging of the barium in the base of the duodenal cap. A series of films showed a typical duodenal ulcer. No five hour examination was done, but in 24 hours all the barium was in the colon. The colon was hyperspastic.



Fig. 3. Traumatic Duodenal Ulcer (in a Child) with Adult-like Deformity.

#### TREATMENT AND COURSE

He was given a modified Sippy powder, with paregoric and bismuth mixture as an antispasmodic. His diet consisted of frequent small feedings of milk, cream, buttermilk, cooked cereals and fruit juices. He did well for two weeks and gained four pounds, when he had a recurrence of diarrhea, probably due to too much magnesia in the powder. He began vomiting and he was brought back. In the hospital he vomited blood and passed stools containing dark blood. He recovered in a few days and is again on the treatment with less powder.

The symptoms of peptic ulcer in children vary with the age of the child. In the newly born, *melena neonatorum* occurs. These ulcers may be said to be acute, and in the age group from one to ten, the symptoms consist of bleeding, loss of appetite, digestive upsets, and occasional perforation. After the age of ten and particularly about puberty, the symptoms of night pain or pain relieved by vomiting, and pain late after meals relieved by more food, or alkalis, or vomiting, resemble the symptoms described by Moynihan. They have seasonal recurrence and pursue the same chronic course as peptic ulcer in adults. When examined the ulcers are found to be deep and round with indurated edges.

Trauma as a cause of peptic ulcer was first described by (1) Potain in 1856. He reported a woman, aged 60, who was struck in the abdomen by a heavy piece of furniture. After 8 years of a clinical history of ulcer, death occurred, and at autopsy a

large, indurated ulcer was found on the lesser curvature of the stomach associated with hour glass deformity.

Traumatic ulcer of the duodenum and the stomach is the subject of an interesting paper by Crohn and Gerendasy in a May, 1933 issue of the Journal of the American Medical Association. They say that there is almost no American literature on this subject but cite many foreign cases of proven traumatic origin.

In discussing the *etiology* they say

the trauma is always of a severe type: falls, violent compression injuries, vehicle accidents, blows from falling bodies, etc. They report the following case: "A man, 35, was struck in the abdomen by the hoof of a horse. A few days later vomiting began. Symptoms continued with increasing severity for one year, at which time gastroenterostomy was performed for a pyloric ulcer. A cure resulted."

The stomach is exposed to injury in the epigastric region where it lies

## ★ Peptic Ulcer Cases become symptom-free

### on the Larostidin Treatment ★

**THE** experience of clinicians who have tested this method shows that, in most instances, Larostidin affords prompt relief.

**After 5 days . . .** Pain usually disappears and does not recur. Nausea, vomiting, hyperacidity, and flatulence are relieved.

**After 10 days . . .** Normal diet well tolerated. Appetite improves. There is consequent gain in weight, general systemic improvement, and vastly improved mental outlook.

**After 24 days . . .** Radiologic findings, in many cases, become negative. Patient can usually be discharged from treatment.

#### One daily injection Larostidin for about 24 days



AMPULS. 5 cc.  
Cartons of 6

\*4 boxes constitute  
one complete  
treatment.

The treatment consists of one daily injection of Larostidin for about 24 days.

Larostidin is a 4% solution of l-erythro-histidine monohydrochloride, supplied in 5 cc. ampuls.

Intramuscular injections are best; the preferred sites for injection are the arms and the gluteal regions.

BULMER, in reporting his results in 52 cases of peptic ulcer (*The Lancet*, Dec. 8, 1934) emphasized the fact that the Larostidin treatment is better than the older methods—alkalies, feedings, etc.—in bringing about complete subsidence of symptoms, and that these results are easily achieved with ambulatory management. Dr. Bulmer's paper was abstracted in the *Journal of the American Medical Association*, February 23, 1935, page 690.

**HOFFMANN-LA ROCHE . . . Nutley, New Jersey**

1. Potain, A: *Bull. Soc. anat. de Paris*, 31: 353, 1856.

within the costal angle, but below the protective border of the liver.

Posteriorly the stomach lies directly in front of the rugged vertebral column. When the stomach, especially when full of food, is pinned between the vertebral column and some obtruding body, or is subjected to great traumatic force, a rupture in the mucosa may readily occur.

(2) A widow, age 44, had been previously free of digestive disease. In February, 1930, when riding in a public conveyance (bus) she was forcibly thrown against the sharp edge of the forward seat on the opposite side of the aisle. The fall was a violent one due to the front wheel of the bus striking a culvert. She was able to proceed home and next day had vague epigastric distress and passed black stools. In twenty-four hours she was nauseated and vomited blood. She had hematemesis and melena for several weeks following. Physical examination showed a contused area below the 9th costal cartilage on the right side. Two weeks after the accident duodenal ulcer was demonstrated by X-ray examination.

It is of interest that the New Jersey Supreme Court in October, 1932, affirmed judgment in favor of the plaintiff.

There is much speculation as to the *mode of ulcer formation*. In experimental work, chronic peptic ulcers are hard to produce and occur only when certain factors are present. Violent trauma is certainly not the cause of a majority of peptic ulcers but it is suggested by many writers that milder degrees of trauma, external or internal, may play a part when changes in secretion, changes in motility or in the nervous mechanism are favorable for the formation of chronic peptic ulcer.

*Pathologically*, traumatic peptic ulcers are usually single, they are usually round, and occur close to the

pylorus, though many have been found about the lesser curvature. They begin as a mucosal or sub-mucosal hemorrhage with laceration of the walls of the stomach of varying degrees of severity. They are more often in the duodenum. Symptomatically, they run a chronic course with digestive symptoms like ordinary peptic ulcers.

Bleeding commonly occurs early in traumatic ulcer.

(3) Liniger and Molineus offer certain postulates that need be satisfied before a case of suspected traumatic ulcer may be accepted as a true example of such a lesion.

1. Proof must be given of the absolute absence of gastrointestinal

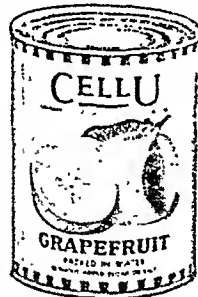
3. Liniger and Molineus, quoted by Gerendasy, Julius: *J. A. M. A.*, 21:1658, 1933.

2. Gerendasy, Julius: Traumatic Duodenal Ulcer. *Am. J. Surg.*, July, 1933.

We desire to obtain one complete Volume One of the American Journal of Diseases and Nutrition. Please write to the undersigned, stating price asked, but do not send the Journals before receiving our reply.

THE PORRO BIOLOGICAL LABORATORIES

718 Medical Arts Building,  
Tacoma, Washington.



## CELLU Canned Fruits

Packed in water without added sugar

INCREASE THE CHOICE OF FRUIT  
IN THE LOW CARBOHYDRATE DIET

### FOOD VALUE

Fruits packed in water without added sugar are shown by chemical analysis to have their carbohydrate content reduced from that of the fresh product. Lessening the carbohydrate content makes it possible to include these fruits in diets where fresh fruits might be prohibitive. We list the carbohydrate values of Cellu fruits here for convenience of comparison.

### CONVENIENT TO USE

Cellu Canned Fruits not only increase the variety in the menu but add much to the convenience of food preparation. Saccharine may be added to these fruits if desired.

Send for Catalogue for Complete Information

Pin to your letterhead and mail  
Send me your new catalogue which contains  
a complete description of  
Cellu Canned Fruits.

D.D.N.-4-25-35



| Carbohydrate Values       |     |
|---------------------------|-----|
| Applesauce ..             | 9%  |
| Apricots ..               | 7%  |
| Blackberries ..           | 7%  |
| Cherries (Red Pitted) ..  | 10% |
| Cherries (Royal Anne) ..  | 9%  |
| Grapefruit ..             | 8%  |
| Loganberries ..           | 7%  |
| Peaches (Yellow Cling) .. | 6%  |
| Pears (Bartlett) ..       | 6%  |
| Pineapple (Sliced) ..     | 12% |
| Pure Plums ..             | 9%  |
| Raspberries (Black) ..    | 9%  |
| Raspberries (Red) ..      | 7%  |
| Strawberries ..           | 6%  |
| Fruit Combination ..      | 9%  |

CHICAGO DIETETIC SUPPLY HOUSE

1750 W. VAN BUREN ST.

CHICAGO, ILLINOIS



A Relapse in Pernicious Anemia is Dangerous

## CHAPPEL'S LIVER EXTRACTS

both Oral and Subcutaneous, are of reliable, uniform potency. Each batch of the latter is tested clinically before being released for sale—an added assurance of its dependability. (Both products are Accepted by the Council of the American Medical Association).

LABORATORIES CHAPPEL BROS, INC.  
ROCKFORD, ILLINOIS

complaints or symptoms prior to the accident.

2. The trauma must be a severe one and localized to the abdominal wall, preferably to the epigastrium.

3. The immediate onset of symptoms must follow the injury.

4. The continuation of the developing symptoms and signs must assume the characteristics of a true gastric or duodenal ulcer.

The paper of (4) Crohn and Gerendasy is reviewed by Dr. Eusterman in the Medical Year Book. (5) Dr. Eusterman and Dr. Joseph G. Mayo report the following case: "A farmer boy, aged sixteen years, was brought to the Mayo Clinic in an ambulance March 18, 1932. Except for mild attacks of influenza and tonsillitis he had enjoyed excellent health until October, 1931, when he had fallen headlong from the back of a moving automobile, striking the epigastrium forcibly on an empty spare tire rack. He was knocked to the ground and was breathless for thirty seconds or longer. At that time

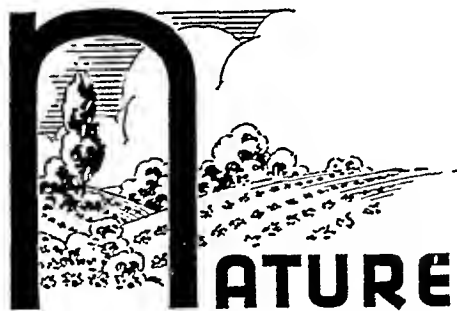
he had experienced no actual pain although there was some contusion of the upper left abdominal wall, and he did not feel well for the remainder of the day. Within twenty-four hours epigastric pain appeared and was most marked on exertion, so that he eventually was compelled to discontinue all work, attendance at school and participation in sports. Aggravation of the pain was not caused by taking food. Shortly after the injury he had had occasional left epigastric pain which appeared half an hour to an hour after meals, lasted for an hour or so, and disappeared before the next meal, so that he was always free of pain at meal time. Five months had passed since the injury, the above symptoms persisting off and on, when, after a day's heavy work on the farm, he had recurrence of epigastric pain and noticed tarry stools. On the two following days he was free of pain. Then the pain became more marked and was associated with thirst, massive hemorrhage from the stomach, syncope and shock. Following this hemorrhage the pain disappeared, and the boy was brought to the clinic.

The patient was pale, in a fair state of nutrition, with no abnormality other than anemia (hemoglobin 68 per cent, and erythrocytes 3,860,000 in each cubic

millimeter of blood) and moderate tenderness, without rigidity, in the left side of the epigastrium. Roentgenoscopic examination March 21, 1932, gave clear evidence of a penetrating ulcer on the lesser curvature, above the incisura angularis. Three days later, after administration of histamine, there was a great deal of secretion, maximal total acidity was 106 units, and free hydrochloric acid, 94 units (titration with tenth normal sodium hydroxide). Because the patient was young and the symptoms of recent onset, operation was deferred and intensive treatment undertaken. He was placed in hospital and made a favorable response. Successive roentgenographic examinations disclosed gradual diminution in the niche, and April 16, 1932, no defect was demonstrable. The boy was dismissed to follow a regimen for ambulant patients with an ulcer. He has been so well since that time that we have not been able so far to get him to return for reexamination although he lives just across the border of a neighboring state."

The above mentioned authors also discuss ulcer as the result of foreign bodies in the stomach and as the result of diaphragmatic hernia.

4. Crohn and Gerendasy: Traumatic Duodenal Ulcer. *J. A. M. A.*, 21:653, 1933.
5. George B. Eusterman and Joseph G. Mayo: Collected Papers of the Mayo Clinic, 25: 68, 1933.

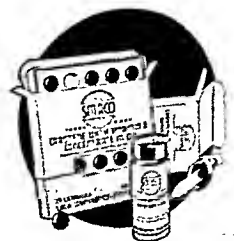


## NATURE OFFERS CAROTENE [PRO-VITAMIN A] IN FRUITS AND VEGETABLES

CAROTENE (PRO-VITAMIN A)  
IS THE MOTHER-SUBSTANCE  
OF ALL VITAMIN A ACTIVITY  
NO FISHY TASTE • EASY DOSES



S. M. A. Corporation offers CAROTENE (PRO-VITAMIN A) concentrated in a vegetable oil vehicle in capsule and liquid forms, alone and in combination with Vitamin D Concentrate. Council accepted.



**S.M.A. CORPORATION • CLEVELAND, OHIO**

# SECTION I—*Clinical Medicine: Diseases of Digestion.*

## Vaccine Therapy in Ulcerative Colitis

### Second Part

*Thesis By*

SIBRAND LUPS (Arts)

GRONINGEN, HOLLAND

*Translated and Edited By*

ABEL J. BAKER, M.D., F.A.C.P.

GRAND RAPIDS, MICHIGAN

### ULCERATIVE COLITIS; A CASE WITH AUTOPSY

*History of Illness:* The patient who was forcibly delivered of her fifth child on April 26, 1933, was admitted to the gynaecological ward on the 4th of May. For some time previous to her confinement she had complained of abdominal pain which gradually grew worse. Her abdomen was larger than it had been during any of her former pregnancies. In the last six weeks of her late pregnancy she had vomited a great deal. There was no particular history of malfunction of her bowels. In spite of the fact that she had lost a great deal of amniotic fluid, her abdomen remained very large *post-partum*. On the 28th of April she developed a temperature. There was very little lochia.

*Examination on the 4th of May.* The patient gives the impression of being seriously ill. Her tongue is moist, not coated. Pulse regular, normal size and tension. Heart and lungs normal. Abdomen is markedly distended, about the size of pregnancy at term. No peristalsis can be made out. Intestinal sounds absent. On percussion there is tympanites and the examination is painful. Palpation of solid organs is impossible because of distension.

*Vaginal examination.* Cervix admits two fingers. Externally the fundus uteri cannot be felt. As far as can be determined, the uterine cavity is empty. There were no tears present. The left appendages apparently are normal. On the right side, there was some resistance which seems to merge into the cervix. The pouch of Douglas was normal. There was no marked discharge. The urine is negative. Temperature runs up to 39° C.

The entire picture gives one the impression of a peritonitis with paralytic ileus altho the etiological connection with her parturition is not clear. She was given physostigmine and bowel irrigations. This treatment relieved her of much distension.

On May 5 her abdomen showed less distension and she passed much flatus. On May 6 her general condition was worse. She complained of severe abdominal pain and vomited everything taken by mouth. Meteorism was marked. Pulse was frequent and small. On May 7, she was continually losing ground. Her face was pinched, the pulse very poor and she was still vomiting. Tongue was red and dry. She was given "cardiozol," digalin and caffeine. Her respiration became more rapid, pulse imperceptible, hands and feet cold, and at 12:30 she died.

*Autopsy by Doctor Behr:* Section was made twenty hours after death and the findings recorded were as follows: On opening the abdomen much gas escaped; cecum, ascending colon and transverse colon were markedly dis-

tended and nearly filled the peritoneal cavity. The coils of the small bowel were also distended although not to the same degree. The serosa was dull with patches of hyperemia and fibrin formation. In spite of the fact that the abdomen contained much gas, there was no perforation found anywhere. About 500 cc. of cloudy free fluid was present. This had no odor. There were no fecal masses present. On removing the ascending colon for a complete inspection, this was torn under the liver and a mass of thin feces flowed into the peritoneal cavity. On opening the small intestine, the mucous membrane was found to be entirely normal. The cecum, ascending colon, and transverse colon, on the other hand, showed many ulcers with a yellow, rather speckled base. The size and form of these ulcers varied a great deal, ranging from a pinhead upward and were found mostly in groups surrounded by mucous membrane which was markedly injected and hemorrhagic in spots. Other ulcers were much larger and of irregular shape. Their greatest width was in the transverse diameter of the bowel. At the site of the ulcers, the intestinal wall was friable and easily torn. The serous aspect revealed many large streaks of fatty tissue. These were also present in the omentum which was adherent to the bowel. The mesenteric vessels were empty. The remainder of the various organs showed no particular changes and the uterus and parametrium were normal.

*Microscopic examination.* Ulcers from the ascending colon showed a complete loss of mucous membrane which was replaced by granulation tissue containing many leukocytes and cell debris, necrotic areas and bacteria. The *muscularis* revealed areas of necrosis. In some places there was marked infiltration of inflammatory nature. In the upper layers of submucosa were found leukocytes and numbers of large mononuclear (abnormal reticular cells) and plasma cells. Such were also found in deeper layers of the intestinal wall as well as large thrombosed veins. The serous aspect was covered with fibrin and leukocytes. Sections of other ulcers revealed similar findings.

Section of the mesentery showed extensive infiltration with many distended mononuclear cells, lymphocytes and a few polynuclears. The tissue was edematous and there was a marked lymphangitis. In some of the lymphatic vessels small cocci were present but whether these were diplococci we were unable to say.

The kidneys showed marked degeneration of the tubular epithelium. There were many small emboli (diplococcus) mostly surrounded by hemorrhages and masses of leukocytes which here and there amounted to small abscesses. The liver cells were swollen and there was much cell dissociation.

(Continued from April, 1935, Issue)

The spleen showed evidence of infection with edema and hyperemia of the pulp. There was marked infiltration with leukocytes. The uterine wall showed many thrombosed vessels but no evidence of inflammation.

From the tissue surrounding the ulcers in the cecum and colon, the *Diplococcus of Barga*n was isolated in pure culture. These organisms were also present in large numbers in the base of ulcers.

#### ANIMAL EXPERIMENTATION BY BARGEN AND OTHER INVESTIGATORS

In 1924, Barga n instituted bacteriological investigations on the material which he isolated from the intestinal mucous membrane of a number of patients suffering with ulcerative colitis. Culturally he found two varieties of microorganism, *gram-positive diplococci* and *gram-negative bacilli*. The diplococci were, but the bacilli were not again identified. (These might have been colon bacilli; Helmholtz and Beele). Inasmuch as it occurred to him that these organisms might possibly be the cause of ulcerative colitis, he carried out animal experimentation to determine their pathogenicity.

For experimental purposes, he used rabbits which had been fed exclusively on vegetables, oats, hay and water. In his first series he used 190 rabbits to which he gave intravenous injections of 2 to 5 cc. of a bouillon culture not over 24 hours old. Some of the rabbits he injected with a mixed culture of both bacilli and cocci, others with pure culture of the diplococci, and still others with a pure culture of the bacilli. Those animals which survived the injection were sacrificed at intervals of from one to 28 days. At autopsy a bacteriological investigation was made of the blood, the mesenteric glands, spleen and in some cases of lesions in the colon.

The results of these experiments were as follows: Of the 190 rabbits, 56 developed lesions in the colon consisting of hemorrhages and superficial ulcers. Of these 56, eleven had been injected with a pure culture of diplococci and 45 with a mixed culture of diplococci and gram-negative bacilli. In those animals injected with mixed culture, the intestinal lesions were more wide spread and were more severe than in those in which the pure cultures were used.

On closer study of the 56 rabbits of which 23 died spontaneously and 33 were sacrificed, it appeared that 38 had developed diarrhea with mucus and blood in the feces. In these, as well as in the others, Barga n found at autopsy colonic lesions and bloody mucus in the feces. In addition to the lesions mentioned, he also found in 15 cases lesions in the ileum. In two he discovered abnormalities in the appendix, in one in the jejunum and in one in the duodenum. All organs in these 56 animals were examined, but except one kidney infarction and one case of hemorrhage in the lumbar muscles no other pathology was found.

In a few animals it was possible to isolate a pure culture of gram-positive diplococci from the mesenteric glands and in a very few from the spleen. Microscopic examination of the affected part of the bowel revealed gram-positive diplococci in the tissues surrounding the lesions. Other bacteria were present only on the surface of these affected areas. In the rest of the 190 experimental animals, 23 developed diarrhea but no discoverable lesions. Sixty-five had neither diarrhea nor any intestinal lesions. Seven developed swelling of the mesenteric glands only. The majority of these

rabbits were injected with cultures of the gram-positive diplococci.

In a number of rabbits, a pure culture of the gram-negative bacilli was injected. These rabbits died within 24 hours after the injection. Intestinal lesions were not found in these cases.

#### CONTROL EXPERIMENTS

In four patients who did not have ulcerative colitis but in whom rectoscopy was done because of hemorrhoids or other conditions, material from the mucous membrane of the bowel was taken for bacteriological examination. From this culture, four rabbits were injected; one of these developed diarrhea and at autopsy petechiae were found in the colon. In cultures from the other three patients, no diplococci were found. Intravenous injections of these cultures into the rabbits caused no bowel lesions.

The results of the first series of animal experiments on the etiology of ulcerative colitis may be summarized as follows: (1) Mixed cultures of the gram-negative "colon bacilli" and the gram-positive diplococci injected intravenously into rabbits, frequently caused lesions of the colon which resembled those which are found in patients suffering with ulcerative colitis. (2) Pathological investigation of the affected areas in the bowel frequently revealed gram-positive diplococci in the tissue surrounding the lesion. (3) Pure cultures of the gram-positive diplococci generally caused no lesions in the colon. (4) Pure cultures of gram-negative bacilli were fatal to the rabbits but caused no changes in the colon.

Barga n explained the results of the experiments as follows: The gram-negative (colon bacilli?) probably caused the illness of the rabbits and in this way created a predisposition to the growth of the gram-positive diplococci. These latter diplococci should then be considered the true cause of disease. Barga n was supported by Helmholtz and Beeler who were of the opinion that colon bacilli might cause edema of the cecum but never actual lesions. In 1925 Barga n and Logan again experimented with 18 rabbits which had been kept for three weeks on a vitamin free diet. Nine of these animals were given 5 cc. of intravenous injections of bouillon cultures of a freshly isolated diplococcus. These animals were sacrificed within 5 days. Autopsy revealed that in eight of these, lesions in the colon had developed, ranging from submucous hemorrhages to small ulcers. Furthermore three animals also had empyema of the gall-bladder which contained a pure culture of the diplococcus. Of the nine animals which had not been inoculated, five died of malnutrition, while four lived for four months on vitamin poor diet.

Cultures of the diplococci obtained from the gall-bladder of those rabbits which had developed empyema were injected intravenously into young dogs. A daily injection of respectively, 12, 20, 20, 20, 20, and 30 cc. was given. Inasmuch as the lesions which Barga n had obtained in his rabbit experiments must be considered more in the nature of an acute condition, he hoped in this manner to produce lesions which would more likely resemble those in the human individual suffering from chronic ulcerative colitis.

Many of the dogs developed serious diarrhea and indeed, on making rectoscopic examinations lesions were found resembling those in the human individual.

Barga n thus succeeded in causing ulcerative colitis



in rabbits kept on a vitamin free diet with a pure culture of gram-positive diplococci. He also succeeded in producing colonic lesions in young dogs with the diplococci obtained from the contents of the diseased gall-bladder in rabbits which had been thus previously injected.

Fradkin and Gray duplicated the work of Bargaen with 4 rabbits. Each animal was given altogether from 40 to 50 cc. of a pure culture of the gram-positive diplococci intravenously. This quantity was given over a period from five to seven days. Two animals developed a frank arthritis. Two others developed diarrhea with marked proctitis. From the rectum of these, diplococci were isolated. These two died at the end of the fourth day. At autopsy dark red hyperemic spots were found in the large bowel. Also here and there pinhead-sized ulcers. The diplococci were found in large numbers in the submucosa of the affected bowel. The heart's blood, mucus from the colon and the gall-bladder also showed pure cultures of the cocci.

Rafsky and Manheim also carried out animal experimentation with the diplococci of Bargaen. They could not produce ulcerative colitis in rabbits. They injected two rabbits intravenously with 4 cc. of a bouillon culture of the organism. The animals developed neither diarrhea nor any other symptoms. Four weeks after injection, they were sacrificed, but at autopsy no anatomical changes were discovered. These experimenters also injected rabbits which had been kept on a vitamin free diet for two weeks with 5 cc. of a pure bouillon culture of the diplococci. These did not develop diarrhea although they lost weight, but remained alive. At the end of three weeks, they were sacrificed. At autopsy they showed no lesions in the colon and no anatomical changes elsewhere.

Gutierrez, Lastra en Blanco injected rabbits intravenously with pure culture of the diplococci of Bargaen. They were unable, however, to produce intestinal lesions, but when a mixed culture of the diplococci and other anaerobic intestinal bacteria was used, the rabbits developed diarrhea and died. At autopsy lesions were found in the colon. These investigators, however, on the basis of their experimentation, deny the etiological importance of the diplococci of Bargaen in producing colonic ulcerative colitis. Rather they feel that anaerobic organisms might have produced these in the animals.

Paulson believes that the animal experiments of Bargaen do not prove conclusively the *diplo-streptococci* to be the cause of ulcerative colitis. Neither does Basler attach to the diplococci of Bargaen any etiological importance.

#### EXPERIMENTAL WORK BY THE AUTHOR

In order to carry on our animal experimentation, it was, of course, absolutely necessary that we secure a culture from an actual case of ulcerative colitis concerning the diagnosis of which there was no question. Further, the diplococcus must necessarily be isolated from the ulcers themselves, inasmuch as similar organisms entirely resembling the diplococcus of Bargaen are sometimes found in the feces of individuals not having ulcerative colitis. For our experiments therefore, we made a culture which was isolated from the colonic ulcers of our case which came to autopsy. Of this material bouillon culture preparations were made and cultured for 24 hours at 37° C. In order to eliminate harmful associations of other bacteria, the cul-

ture was centrifuged. The clear upper layer was separated and replaced with physiologic salt solution in which the bacteria again were suspended. This was again centrifuged and the upper layers removed. This was repeated twice. Finally a concentrated emulsion in physiologic salt solution was used for animal injection. Further tests were made with emulsions of this culture after passage through one or more animals. In our experiments we used rabbits which were normally fed.

*Experiment with rabbit No. 1.* Weight 3 kg. 1½ cc. of the above diplococcus emulsion injected in the vein of the ear.

There was no diarrhea, sacrificed after 7 days. *Autopsy:* large bowel in some areas showed bloody mucous membrane. From the bowel wall material was taken and cultured. Diplococcus was positive. In the lumen of the large bowel a number of small cyst formations somewhat smaller than a green pea were present. The contents of these on culture show a pure strain of diplococcus. Small bowel is normal, gall-bladder filled but negative for diplococcus.

*Experiment with rabbit No. 2.* Weight 3 kg. 1 cc. of diplococcus emulsion injected into vein of ear, after passage through another rabbit.

There was considerable loss of weight but no diarrhea; sacrificed after 11 days. *Autopsy:* large bowel very hyperemic with much mucus. In two areas at the site of branching of the small blood vessels were found small grayish-white circumscribed elevations about 1 cm. in diameter. Small bowel normal. Gall-bladder filled, diplococcus positive. Peritoneal glands swelled, diplococcus positive. Spleen soft.

*Experiment with rabbit No. 3.* Weight 3 kg. 1 cc. of diplococcus emulsion injected into the vein of ear after previously passing through two rabbits.

Much loss of weight, no diarrhea. Died in 8 days. *Autopsy:* large bowel had much mucus. In one area at the site of small branching blood vessels were found grayish-white sharply circumscribed, rather round elevations with diameter 1 cm. From this tissue the diplococcus was cultured. Small bowel was normal. Gall-bladder was normal. Bile was negative for diplococcus. Spleen soft.

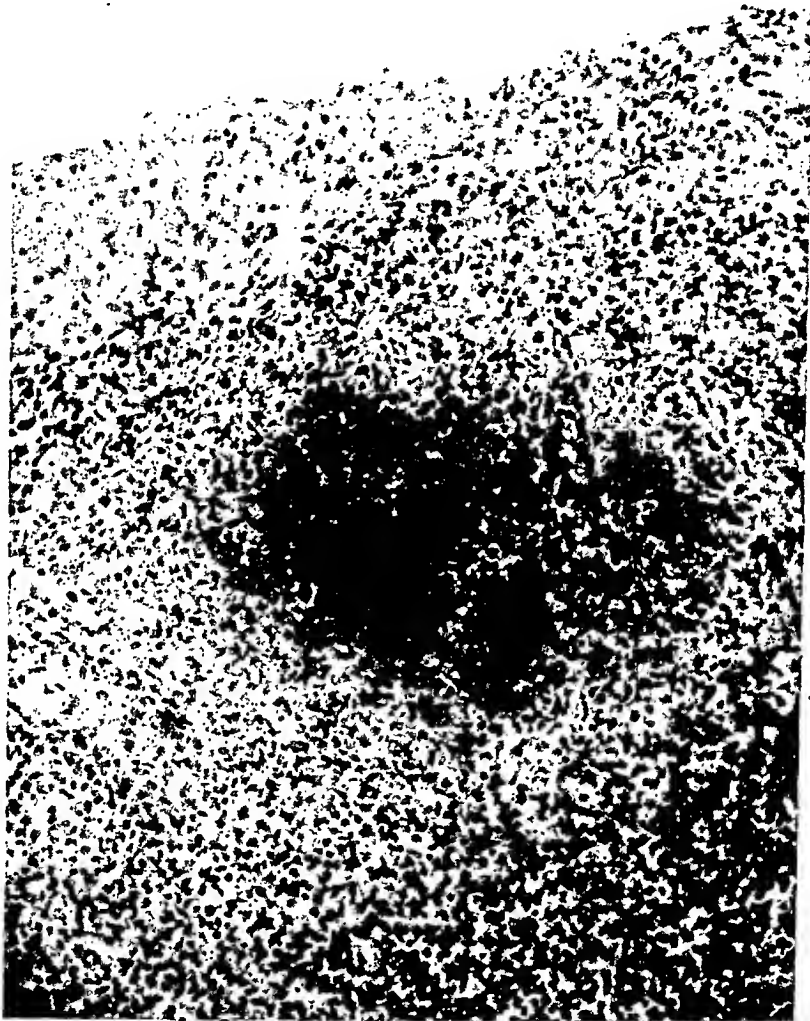
*Experiment with rabbit No. 4.* Weight 2 kg. 1 cc. original diplococcus emulsion injected into vein of ear. Rabbit became ill after 2 days with diarrhea and died after 8 days. *Autopsy:* large bowel markedly injected, and in the lumen much bloody mucus. Diplococcus positive. Stomach and small bowel show injected mucosa. Gall-bladder acutely inflamed. Diplococcus positive.

*Experiment with rabbit No. 5.* Weight 1¼ kg. 1 cc. original diplococcus emulsion injected into vein of ear. Much loss of weight. Ill in few days with diarrhea. Died after 7 days. *Autopsy:* mucous membrane of large bowel and cecum markedly hyperemic; some areas showed much bloody mucus. Diplococcus positive. Stomach and small bowel also were markedly hyperemic. Gall-bladder filled. Bile negative for diplococcus. Spleen soft.

*Experiment with rabbit No. 6.* Weight 1½ kg. 1 cc. original diplococcus emulsion injected into vein of ear.

After two days there was diarrhea and much mucus discharge. Died in 5 days. *Autopsy:* part of large bowel showed punctate hemorrhages. There was also much bloody mucus. Diplococcus positive. The remainder of the large bowel was also hyperemic, likewise the small bowel. Gall-bladder filled. Diplococcus positive. Spleen soft.

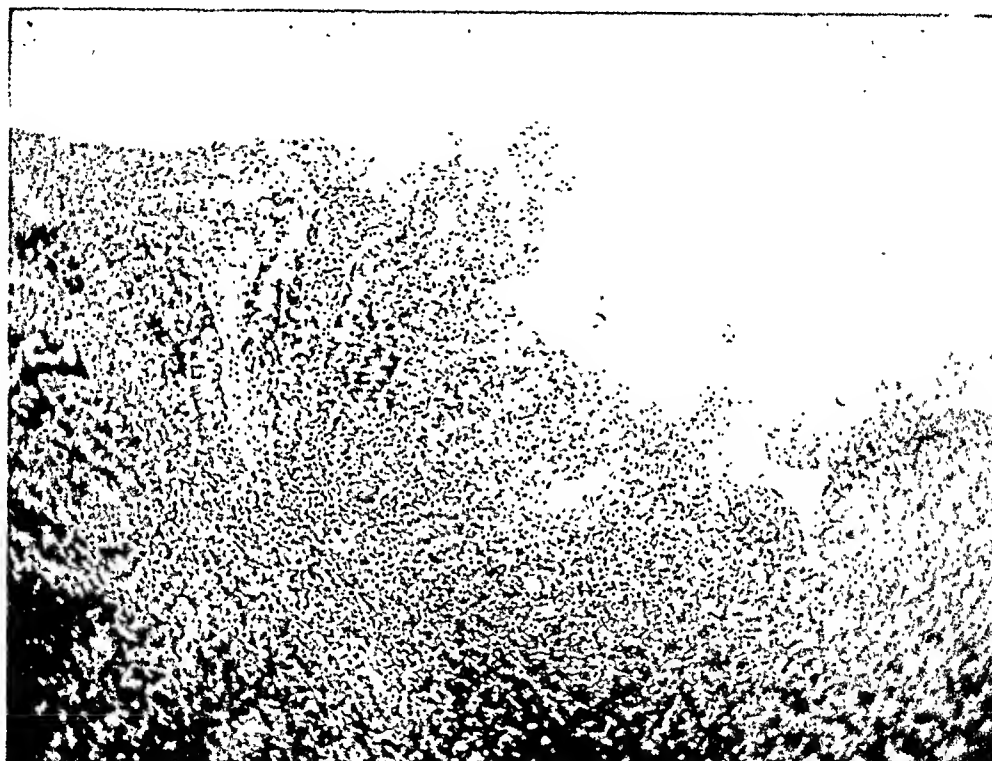
*Experiment with rabbit No. 7.* Weight 1 kg. 1 cc. original diplococcus emulsion injected into vein of ear. The rabbit was sick after two days with diarrhea and mucus discharges. Died in 5 days. *Autopsy:* mucous membrane and cecum showed much swelling and hyperemia. In the lumen there was much bloody mucus. Diplococcus positive. Small bowel hyperemic. Much mucus in the lumen.



---

Fig. A. Rabbit No. 14. A small focus containing tissue and cell debris found in an inflamed joint capsule. Much nuclear fragmentation. Oil immersion magnification reveals many diplococci.

---



---

Fig. B. Mucous membrane of colon; rabbit No. 2. Below the surface large accumulation of lymphocytes. Mucous glands are separated by widespread infiltration of inflammatory cells. Some areas show an entire absence of mucosa which is replaced by inflammatory infiltration containing many lymphocytes and leucocytes.

---

Gall-bladder normal. Diplococcus negative. Spleen soft. Diplococcus positive.

*Experiment with rabbit No. 8.* Weight 1 kg. 1 cc. original diplococcus emulsion injected into the vein of ear. There was diarrhea with bloody mucus discharges, and the rabbit died within 5 days. *Autopsy:* on opening the abdomen both cecum and large bowel were markedly distended, red and transparent. Lumen filled with bloody mucus. The mucosa shows marked swelling and desquamation. Mucus was positive for diplococcus. Small bowel was hyperemic. There was much mucus in the lumen. Diplococcus positive. Spleen soft. Urine purulent, and the diplococcus was positive. Gall-bladder normal, diplococcus was negative. (See micro-photograph).

*Experiment with rabbit No. 9.* Weight 1 kg. 1 cc. original diplococcus emulsion injected into vein of ear. The rabbit was sick after 3 days with diarrhea and died in 4 days. *Autopsy* not done.

*Experiment with rabbit No. 10.* Weight 2½ kg. 1 cc. original diplococcus emulsion injected into vein of ear after passage through 3 rabbits. Ill in 4 days with diarrhea and died in 10 days. *Autopsy:* large bowel hyperemic. Small bowel for a distance of about 30 cm. was covered with pinhead-sized grayish-white markedly circumscribed elevations.

The remainder of the mucosa was hyperemic. Stomach wall covered with mucus. Mucosa hyperemic. There were abscesses in the liver. Diplococcus was positive.

*Experiment with rabbit No. 11.* Weight 2½ kg. 1 cc. original diplococcus emulsion injected into vein of ear after passage through 4 rabbits. Rabbit was ill after 6 days with diarrhea and died in 10 days. *Autopsy:* part of large bowel mucosa swollen and hyperemic. Lumen was filled with bloody mucus. Diplococcus was positive. Stomach and small bowel mucosa hyperemic. Gall-bladder shows empyema. Diplococcus was positive. Spleen soft. Lungs show evidence of inflammation.

*Experiment with rabbit No. 12.* Weight 1 kg. 1 cc. original diplococcus emulsion injected into vein of ear. There was diarrhea in two days. Feces slimy. The rabbit died in 7 days. *Autopsy:* mucosa of large bowel hyperemic. Much mucus in the lumen. Diplococcus was positive. Mucosa of small bowel hyperemic with area of about 20 cm. long covered with pinhead-sized markedly circumscribed grayish-white elevations. Much mucus in the lumen. Diplococcus positive.

*Experiment with rabbit No. 13.* Weight 2 kg. 1 cc. original diplococcus emulsion injected into the vein of ear. Rabbit became ill in few days. There was diarrhea later, and the animal died in 8 days. *Autopsy:* mucosa of large bowel hyperemic with many punctate hemorrhages. Bloody mucus in the lumen. Diplococcus positive. Small bowel hyperemic, markedly so in small areas. Gall-bladder normal. Diplococcus negative. Spleen was soft.

*Experiment with rabbit No. 14.* Weight 4 kg. 1½ cc. original diplococcus emulsion injected intravenously. The rabbit was ill in one week, later recovered but developed arthritis in 2 joints. After lapse of two months, it died. *Autopsy:* pus found in joint cavities. From one of these diplococcus was cultured. (See micro-photograph).

*Experiment with rabbit No. 15.* Weight 4 kg. 1½ cc. original diplococcus emulsion injected intravenously. Rabbit not ill after 2½ months but arthritis developed in two joints. Pus from these joints was negative for diplococcus. The other organs showed no abnormalities.\*

#### CONTROLS

Experiments were carried out on groups of 4 to 5 rabbits which were chosen from a number of healthy animals.

\*For assistance in the histological examinations, I desire to thank Dr. Behr most heartily.

Those not injected remained perfectly well. Two of them were sacrificed and at autopsy revealed no departure from the normal mucous membrane of the bowel. Other rabbits were injected with diplococcus obtained from the feces of individuals not having ulcerative colitis. These animals also remained perfectly well and the intestinal mucosa showed no abnormalities.

The diplococci isolated from the diseased intestines of the experimental animals proved to have the same characteristics including agglutination properties as the original strain. Histologic examination of the affected intestinal areas was made in a majority of the autopsied animals. Inasmuch as a few rabbits (belonging to one group) appeared to have coccidiosis, it made the histological study of our specimens more difficult. In other rabbits in which no coccidiosis existed, there were very clear-cut departures from the normal mucosa. These consisting at times of swelling and hyperemia, and in other cases of exudation with fibrin and round cell infiltration containing some leukocytes.

Desquamation of the mucosa was present in some cases and in one necrosis was present in the superficial layers. Some of these changes are characteristically shown in the accompanying micro-photographs of rabbit No. 2 and No. 8.

#### SUMMARY OF THE RESULTS

The clinical symptoms displayed by the injected rabbits consisted of rapid loss of weight and in most animals a diarrhea. In nearly all the rabbits after 48 hours the diplococcus was present in the blood stream. After 72 hours, however, they had disappeared. At autopsy marked swelling of the mucosa with a high degree of hyperemia was present. This was particularly true of the large bowel. In the vast majority of cases bloody mucus was seen in the lumen and sometimes in that of the cecum and small bowel. From this material the diplococcus was isolated quite regularly. Histological examinations of the affected tissues have already been mentioned. At times there was empyema of gall-bladder and the culture in these was always positive for diplococcus. Even in those gall-bladders in which the contents showed no macroscopic changes, the diplococci were found. In only one case was there pyuria and it was possible to isolate the diplococci from the contents of this bladder. In all other cases the urine was clear and negative for diplococci. The mucosa of stomach and small bowel frequently was hyperemic. The spleen in nearly all cases was soft and the splenic tissues was positive for diplococci. In one rabbit there was an inflammatory process in the lungs. The other animals, however, showed no abnormal conditions in the respiratory tract. In one case abscesses were found in the liver and pus from these was diplococcus positive. (See table in connection with Author's experiments).

#### CONCLUSIONS

The fact that at autopsy of the experimental animals, the diplococcus was nearly always constantly present in the bloody mucus which covered the swollen hyperemic mucous membranes, and that the histological examination of this structure plainly showed marked pathological changes, leads us to the conclusion that the diplococci intravenously injected have a predilection for the bowel and are able there to initiate a disease process. Even in those rabbits which died or were sacrificed within a few days after the injection



Fig. C. Mucous membrane of colon; rabbit No. 8. Photograph shows rather large mucous fold. Except for a few gland cells the mucosa is thinned and desquamated. In the mucous membrane and to a small degree in the submucosa many inflammatory cells. Marked hyperemia.



---

Fig. D. Diplo-streptococci of Bargen.

---



tion of the diplococcus emulsion and which showed the least pathology, one always found rather wide-spread departures from the normal bowel. The X-ray examinations of the bowel (see section on X-ray) and the examinations of the feces of those patients having the early stages of chronic ulcerative colitis justify the opinion that in these cases, the early stage of the affection is a catarrhal one and ulceration may be expected only in the later stages.

### SYNOPSIS

In a patient who died of ulcerative colitis, the diplococcus of Bargaen was isolated from intestinal ulcers. Material from these ulcers was at once taken and made into an emulsion which after 2 or 3 washings was injected into healthy, normally fed rabbits. In the majority of these rabbits, the clinical picture of enteritis appeared and they died within 5 to 10 days after the injection. From mucus of the intestinal wall particularly of the colon which, as a rule, was bloody, the diplococcus was regularly isolated. The histological examination of these areas of the mucosa revealed marked inflammatory changes.

Control animals remain entirely well. A few which were autopsied revealed normal conditions in the bowel. The diplococcus was never found in these rabbits nor was it present in those animals which were sacrificed for other reasons. The difference between our animal experiments and those of Bargaen and others is likely explained by the fact that the cultures isolated from the ulcers of our patient at operation possessed an unusual virulence. (See Table 1).

The results of our work lead us to the conclusion that the diplococcus is able to develop inflammation of the cecum and colon.

### SUMMARY OF OBSERVATIONS

As has been mentioned, Bargaen originally succeeded in producing colonic lesions in healthy rabbits only with a mixed culture of diplococci and a gram-negative bacilli. Later he was able to produce the same results with pure culture of diplococci, providing the rabbits had been given vitamin poor nourishment. Fridkin and Gray duplicated these experiments of Bargaen in 4 rabbits. At autopsy they found colonic lesions in two of these animals. Gutierrez, Lastra en Blanco could not produce lesions with pure culture of diplococci in rabbits which had been normally fed. They succeeded, however, in producing colonic lesions when they used a mixture of diplococci and anaerobic intestinal organisms. In our opinion these experiments are entirely in line with the first experiments of Bargaen.

Rafsky and Manheim were unable to produce colitis in 4 rabbits which had been fed on a vitamin free diet, with a pure culture of diplococcus. However, other factors such as the variety of the experimental animals and the virulence of the culture may influence the results of the experiments to quite a degree. In our opinion, the results of this work upon only 4 rabbits cannot be considered sufficient argument to question the pathogenicity of the diplococcus. We have succeeded in producing in the laboratory of the Groningen Clinic the same bowel changes in rabbits as the investigators mentioned although in contrast with

their work, we did not use mixed culture but only pure culture of diplococci, and our animals were not given vitamin poor diet but were fed normally.

The question arises why if Bargaen could prove the virulence of the diplococci in rabbits only after they had been placed on a vitamin poor diet for three weeks, were not other investigators successful in their attempts. To this I would give the following answer: The fact that their experiments did not give more positive results points to the possibility that the virulence of these organisms might diminish quite rapidly. It is a well known fact that this is peculiar to many other pathogenic organisms. Rapid isolation and probably extraordinary virulence of our cultures in all likelihood had a favorable influence on the success of our work. These experiments were performed in a very brief period after we succeeded in isolating the diplococci.

### AFTER-TREATMENT

It may still be emphasized that the alleviation of subjective symptoms and the disappearance of pathological elements from the stools do not in any way signify anatomical restoration of the diseased bowel. Rectoscopic and roentgenologic examinations very plainly indicate that this can be expected only after months have elapsed. This is also proven in those cases in which ileostomy and colon irrigations were used. In order to expect continued success from the treatment which has been used, one must exercise the utmost care in the after treatment. This should, leaving active therapy out of consideration, not materially differ from that used in the acute stage of the illness. For those in poor social circumstances, a long stay in a clinic is very desirable.

If the patient comes under the insurance laws, which in our series frequently was the case, the assurance that he will again be able to resume his occupation must be emphasized. Information given to the family doctor generally will take care of difficulties arising in this respect.

Naturally we must not expect, in cases which show marked pathological changes in the colon in which the elasticity may be completely lost, that vaccinations or any conservative therapy will be followed by complete anatomic restoration. In such very advanced cases, we must be satisfied if the case has progressed to a point where the patient's condition is such that his existence will be fairly comfortable. Circumstances, of course, may make it advisable to refer him to the surgeon.

### SUMMARY

During the years 1925 to 1931, Bargaen of the Mayo Clinic at Rochester successfully treated a large number of patients having ulcerative colitis, with autogenous vaccines made from diplococci isolated from the intestinal ulcers found in his cases. On the basis of animal experimentation he considered these organisms the etiological factor in this disease and obtained favorable results by using vaccine therapy.

A number of investigators questioned the pathogenicity of these cocci and therefore did not accept Bargaen's conclusions. There is still much controversy on this question in the literature. One weak point in Bargaen's animal experiments on the pathogenic properties of the cocci was, among others, the fact that before the injection of cocci, the animals had been kept on a vitamin poor diet for 3 weeks.

*Summary of experiments with rabbits injected intravenously with a pure culture of diplococcus:*

| No. | Weight Kgs. | Diarrhea                                       | Died or Sacrificed | Condition of Colonie Mucous Membrane                                                 |
|-----|-------------|------------------------------------------------|--------------------|--------------------------------------------------------------------------------------|
| 1   | 3           | —                                              | Sacrificed—4 days  | Bloody-Diplococcus positive                                                          |
| 2   | 3           | —                                              | Sacrificed—11 days | Swelling and hyperemia, enlarged lymph follicles-diplococcus positive                |
| 3   | 3           | —                                              | Sacrificed—11 days | Swelling and hyperemia, enlarged lymph follicles from which diplococcus was cultured |
| 4   | 2           | +                                              | Died—8 days        | Mucosa markedly infected, diplococcus positive                                       |
| 5   | 1½          | +                                              | Died—7 days        | Hyperemia, Diplococcus positive                                                      |
| 6   | 1½          | + mucus                                        | Died—5 days        | Hyperemia and punctate hemorrhages Diplococcus positive                              |
| 7   | 1           | + mucus                                        | Died—5 days        | Swelling and hyperemia, diplococcus positive                                         |
| 8   | 1           | + Blood & mucus                                | Died—5 days        | Swelling and marked hyperemia, Diplococcus positive                                  |
| 9   | 1           | +                                              | Died—4 days        | No autopsy                                                                           |
| 10  | 2½          | +                                              | Died—10 days       | Hyperemia, swollen lymph follicles Diplococcus positive                              |
| 11  | 2½          | +                                              | Died—10 days       | Swelling and hyperemia, diplococcus positive                                         |
| 12  | 1           | + mucus                                        | Died—7 days        | Hyperemia, numerous swollen lymph follicles, Diplococcus positive                    |
| 13  | 2           | +                                              | Died—8 days        | Hyperemia and punctate hemorrhages Diplococcus positive                              |
| 14  | 4           | Arthritis after 2 mo. Diplococcus positive     |                    |                                                                                      |
| 15  | 4           | Arthritis after 2 mo. Negative for diplococcus |                    |                                                                                      |

It is rather remarkable, as far as we could ascertain from the literature that Barger's vaccine therapy on the whole has been used very little in Europe. It occurred to us rather desirable, therefore, to make further investigations on the subject. Animal experiments were carried out as follows: Pure cultures of diplococci isolated from the ulcers of a typical case of *colitis ulcerosa* which came to autopsy were injected into a number of rabbits which had not been kept on a vitamin poor diet. These injected animals developed diarrhea and at autopsy very distinct pathological

changes were found in the intestinal mucosa. The bloody mucus which generally filled the intestine contained the diplococci in large numbers. These findings placed Barger's contention concerning the pathogenic properties of the diplococci on a firmer basis.

In our investigations X-ray studies of the intestine were very carefully made. Among other things, X-ray films of pathological and non-pathological intestines were compared with the actual anatomical picture. In this way it was made possible to point out pathological deviations which had been formerly overlooked. Regarding the success of the vaccines which were used in the Groningen Clinic (and by some physicians who obtained vaccines from us) it may be remarked that no fewer than 8 out of our 16 patients recovered completely. Six patients were considerably improved and in 2 cases the results were not particularly good. The results therefore justify to a high degree the use of vaccine therapy in cases of ulcerative colitis. Considerable difficulty has also frequently been encountered in the isolation methods used hitherto. We, therefore, adopted a method used by Doctor van der Zoo de Jong which enabled us to obtain pure cultures of these microorganisms in a very easy manner.

#### CASE HISTORIES

**CASE 1.** Mrs. M. V., aged 29, married, entered the Clinic April 22, 1933. Always well until a year ago when she began to have cramp-like pains preceding each bowel movement. No pain during or after defecation. Averaged 3 stools per day; these were mushy and mixed with blood and mucus. Treatment by family physician gave some relief but her pain did not completely disappear. Six months ago there was an increase of blood and mucus in her stools which averaged about 4 per day. Until 7 weeks before entrance there was no change in her condition. She then developed "grippe" and defecated more frequently. Two weeks ago she thought there was some improvement and considered that her stools looked some better. During the past few months there was much fatigue before menstruating. At such times she had much headache. Appetite was good and there was no loss of weight.

**Physical examination:** Patient gives one the impression of being somewhat nervous but otherwise well. Mucous membranes of good color, tongue clean. Papillae not atrophic. She has one carious tooth. Tonsils normal. Pulse normal. Lungs normal. Examination shows a faint systolic murmur over all valve areas, not heard so well after exercise. Abdomen is soft. Parenchymatous organs not felt. No abdominal resistance and no tenderness. Intestinal sounds normal. Rectal mucosa feels thick and the finger when withdrawn is bloody.

**From the notes on April 27:** The first two days no defecations; on the fifth and sixth day there were 3 to 4 daily stools which were large and mushy consisting mostly of blood and mucus. She has continuous abdominal pains which are more intense before defecation.

Feces negative for dysentery. Large numbers of Barger's diplococci present. Blood: H.b. 58 Sahli; erythro. 4,200,000; leuc. 8900. Differential count; baso. ½%; eos. 1%; trans. 10; polys. 55½; small monos. 26; large monos. 7. Sedimentation after 1 hour 50 mm. Wassermann negative.

April 29: Rectoscopy (12 cm.). Mucosa swollen and very hemorrhagic.

May 2: Test meal: Free H.C.L. 37; total acidity 72. No diplococci could be cultured from the stomach contents.

May 3: Barium enema: Lower part of descending colon shows no haustration; contour reveals an irregular saw-toothed appearance.

May 4: No gram-positive diplococci could be cultured from the duodenal bile.

May 6: Three to four defecations daily; much bloody mucus mixed with the feces.

May 9: Vaccine therapy begun. She was given high caloric diet. No coarse food stuffs allowed.

May 11: Defecates 4 times daily mostly blood and mucus.

May 19: One to two movements daily consisting of blood, mucus and feces. Occasionally less blood and mucus.

May 19, 20, 21: Pre-menstrual temperature rise up to 38.5° C.

May 24: Blood: H.b. 54 Sahli. Two defecations daily; less blood and mucus than on entrance. Some parts of stools show no blood or mucus.

June 24: She feels very much better, wants to sit up. Stools thick and mushy but still contain some blood and mucus. Sensitization tests, (Storm van Leeuwen) intracutaneous; human skin, moulds, mites and horse, weakly positive.

June 20: Feces thick and soupy, some portions show no blood or mucus to the naked eye.

June 23, X-RAY EXAMINATION: After introducing air in the colon, the renal flexure and descending colon revealed a granular aspect.

From the time that the vaccine was given in quantities of 0.8 cc. the patient reacted with a temperature increase up to 38° C, sometimes to 38½° C at which time she feels ill and has headache. Between injections her temperature ranges around 37 C.

June 28: Bowels move once or twice daily. Feces now show normal formation. Macroscopically no blood or mucus. Microscopically particles of mucus.

July 4: Stools normal. No marked temperature rise after vaccination.

July 11: She feels well. Carious tooth extracted. Bowels move daily. Stools are normal and contain no pathological substances. Temperature in the intervals between vaccinations averages 37.5 C. After vaccinations this rises 0.3° to 0.4° C. Blood: H.b. 62 Sahli. She was dismissed. The same therapy to be continued by family doctor. Was given Bland's pills for anemia.

August 15: (Report): Doing her housework but this brings on fatigue. The feces are normal with no blood and mucus. Vaccine discontinued.

August 29: Still fatigued after work. Feces macroscopically normal. Microscopically mucus. Blood: H.b. 72 Sahli. Sedimentation test after 1 hour 14 mm.

X-RAY ("umbrathor"): Contrast mass reaches the small bowel. Descending colon shows only little haustration. Mucosa of hepatic flexure shows some evidence of intestinal folding but the transverse and descending colon none. Mucous membrane appears swollen. Patient is advised to stop all housework.

December 26: Because of social conditions, patient has been obliged to do much work. For a couple of weeks, again has thick mushy stools with blood and mucus, about 2 to 3 per day. Has more pain. Absolute rest ordered. Vaccinations again prescribed.

February 28, 1934: Condition the same as in December. Has been unable to rest. Family doctor was written about her condition. Vaccinations stopped. Blood: H.b. 62 Sahli. Was given 1 gram *ferrum reductum* 3 times per day.

April 20: She has rested since March, general condition much better. Defecates 2 or 3 times per day. Stools thick and mushy, some blood and mucus. Still has abdominal pain before each stool. Blood: H.b. 68 Sahli; leuc. 9000; differential count, eos. 1; trans. 7; polys. 58; small monos. 29; large monos. 5.

Results of vaccinations: Rapid improvement at first so that in 9 weeks the subjective complaints disappeared and the feces showed no more pathological elements. However, after about 4 months her condition grew worse which, in our opinion, must be attributed to the unsatisfactory after treatment.

CASE 2. Mr. J. B., aged 15, student in a technical school admitted to the medical clinic January 15, 1933. He was suddenly taken ill in November, 1932, with diarrhea, averaging 10 thin watery stools per day. Each defecation was preceded by severe pain in lower abdomen. During the defecation and afterwards there was no pain. Feces showed blood and mucus. He never vomited. Does not know whether or not he had fever. He remained in bed the first 4 days of his illness, then got up. Appetite at this time fairly good. No other illness of this type in his community. The family doctor prescribed different remedies without any relief. Gradually condition improved. Frequently of bowel movements was lessened. Stools gradually changed from watery to mushy and abdominal pain which preceded defecation improved and finally ceased. One week before admittance, he was having an average of one daily stool which was thick and soupy, occasionally fairly well formed but still contained some mucus and had a very disagreeable odor. There has been no perceptible loss of weight. He had measles and whooping cough in childhood, also tonsillotomy.

From the notes: He is of normal build and gives one the impression of not being ill. Pulse normal, mucous membranes good color. Tongue is moist, not coated. No atrophic papillae. Teeth are sound. Tonsils are normal. Heart and lungs normal. Liver and spleen not palpable. Intestinal loops not felt. No abdominal tenderness. No excessive abdominal noises. Rectal mucosa feels normal. Examining finger shows no blood.

January 23: Bowels move 2 or 3 times daily. Stools normal in color, shape and consistency. No occult blood. Microscopically there is some mucus. Bacteriological examination negative for dysentery.

January 26: Rectoscopy is negative.

January 27: Examination of fractional meal, 5 4; 2 8; 6 12; 16 22; 20 21; 15 25; 22 32; 24 36; 35 50.

January 28: Roentgen photos after injection of air. Hepatic flexure reveals granular aspect.

February 10: Stools now number only one per day. Microscopically mucus. Rectal temperature never over 37.6° C.

February 12: Dismissed.

April 4: (Report): Developed diarrhea one or two weeks after dismissal. Abdomen not tender. Rectal examination negative. Feces to be sent.

April 15: Feces mushy, much bloody mucus and very offensive odor. Microscopically nothing new. Negative for dysentery. Diplococcus of Bagen present in large numbers. Vaccine prepared.

April 29: Still has frequent abdominal pain. Defecates 4 times a day. Stools thin and mushy, much mucus and very disagreeable odor.

Blood: H.b. 76 Sahli; erythro. 5,200,000; leuc. 7,000; differential, baso. ½; eos. 1½; trans. 8; polys. 62; small monos. 20; large monos. 8. Sedimentation after 1 hour 30 mm.

First injection of autogenous vaccine administered. Vaccine to be continued by family physician. General diet but no coarse food stuffs.

January 13: (Report): At first condition unchanged but later there was improvement. The abdominal pains disappeared, stools became firmer in consistency and occasionally were normal. Some blood and mucus at times.

X-ray films of bowel: Hepatic flexure and transverse colon reveal much swelling of mucous membrane. Upper descending colon reveals only transverse folding.

July 11: (Report): Original condition about as it was on June 13. One week ago stools again became thin and more numerous, preceded by abdominal cramps. Feces thick and mushy. No macroscopic mucus. Microscopically mucus is present.

August 8: (Report): No complaints. Bowels move daily. Normally formed stools, negative to naked eye. Laboratory reports no pathological elements. Blood: H.b.

80 Sahli. Sedimentation after 1 hour 8 mm. Vaccination discontinued.

October 5: (Report): No complaints, has daily stools, normally formed. Negative for diplococcus of Bergen.

December 15: He has been entirely well; stools remain normal.

March 20, 1934: Feels entirely well. Stools normal.

*Final comments on vaccinations:* After about 12 weeks all subjective complaints have disappeared, stools were normal and contained no pathological elements. His condition has remained satisfactory up-to-date.

**CASE 3.** Mr. J. P., aged 45, factory worker, admitted to the surgical clinic December 30, 1930, with following complaints: For the past year he has had continual pain in lower abdomen which became worse just before defecation and persisted during the bowel movement. At first stools contained some blood, later also mucus and pus. He had frequent urge to defecate. Several times a day a fairly large quantity of blood, mucus and pus was expelled. He frequently had painful rumbling in his abdomen which improved after passing flatus. During the preceding few months before admittance there was some improvement in his condition.

*From the notes:* Generalized tenderness over left lower abdomen. Rectal palpation is somewhat painful but reveals no special findings. Examining finger is bloody.

*Rectoscopy* (15 cm.): Intestinal wall at this distance from the anus is covered with mucus. After removal of this, the mucosa looks markedly hyperemic.

January 8, 1931: Persistent blood in the stools.

January 9: X-ray examination confirmed the diagnosis of ulcerative colitis. The process is localized in the lower part of descending colon and in the sigmoid.

January 20: *Appendicostomy* is done. For first few days post-operative, the colon was irrigated with weak tea once a day.

January 29: About 1 cm. of the protruding appendix has become necrotic. This was removed and a drain attached to the stump.

March 2: No complaints. The fistula functions well. Temperature normal. Bowels move daily. Feces still show blood.

March 14: Stools not yet entirely formed, reddish brown in color and still contain occult blood.

March 31: Occasionally stools are negative for blood.

April 8: Drain removed.

April 11: Rectoscopy revealed no blood or mucus. Mucous membrane looks velvety. Patient dismissed.

May 12, 1931: (At the Poliklinik): Patient has regular daily stools, no blood or mucus in feces. Still has fistula resulting from appendicostomy. This shows very little discharge.

July 13: Patient has developed hernia in operation scar. This still discharges. He is about to resume his work.

October 13: Patient has daily normal stool, negative for blood and mucus.

*Rectoscopy:* The lower 10 cm. of the mucosa looks normal, above that it is a little swollen and there is much mucus attached to it. No bleeding or ulcers observed.

December 10: No complaints: Bowels move regularly and stools are normal.

*Rectoscopy* (15 cm.): Mucous membrane still looks velvety.

March 16, 1932: The operative scar shows a small hernia with a bit of granulation tissue protruding. Patient is doing his work.

May 3, 1932: Stools again contain much blood.

*Rectoscopy:* Rectal mucosa bleeds slightly. Patient referred to medical department for vaccine treatments.

May 24: Patient admitted to medical department. Since May 3 the stools have gradually become more bloody. Abdominal pain before and during defecation. Otherwise

patient feels fairly well, is not unduly fatigued and has good appetite. No loss of weight.

*From the notes:* Gives the impression of being well. Tongue slightly coated; no atrophic papillae. Teeth are well taken care of. No caries. Tonsils apparently negative. Heart and lungs normal. In the lower right quadrant, there is an oblique operation scar about 10 cm. long. On the left, can be felt a somewhat tender loop of gut running vertically and about the thickness of one inch. In this vicinity, one frequently can hear intestinal rumbling. The right testicle is enlarged and tender.

*Rectal examination:* The rectal mucosa feels thick. Slight pressure with finger elicits pain. Examining finger shows blood on withdrawal.

May 27: Defecates once or twice daily. Stools show largely blood, mucus and pus. Inasmuch as the patient feels constipated, a soap suds enema was given. This brings some hard fecal masses. During the day on several occasions, rather purulent matter was excreted.

*Examination of stomach contents 45 minutes after test meal:* No free HCL, total acidity 38. No pepsin, no lactic acid. Stomach contents reveal no gram-positive diplococci.

*Blood:* H.b. 68 Sahli; erythro. 4,200,000; leuc. 8,200; differential, immature cells 1%; trans. 14; polys. 64; small monos. 18; large monos. 3. Sedimentation test after 1 hour 48 mm. Wassermann negative.

June 1: During last few days defecates twice daily. Stools a mushy mass consisting of mucus, blood and particularly pus. Some portions contain hard masses of feces. Examination of stool was negative for dysentery but revealed large numbers of Bergen's diplococci. Autogenous vaccine made. Rectoscopy (12 cm.) revealed a bloody swollen mucosa.

June 2: *X-ray films* ("umbrathor"): Sigmoid colon rather stiff; haustration practically absent. Mucosal shadow reveals only coarse transverse folding in the distal part of the transverse colon. The sigmoid shows irregular mucosal fold formation. No longitudinal folds.

June 6: Autogenous vaccinations begun. Patient was given acidol-pepsin, vitamin rich diet but no milk. Coarse foods and substances leaving much residue not allowed.

June 13: Sensitization reactions (Storm van Leeuwen) cutaneous, positive for cat. Intra-cutaneous weakly positive, for human skin.

Daily stools for the last few days consisted of a rather purulent mass mixed with some solid portions of feces. Inasmuch as patient complained of feeling rather "full" he was given an occasional enema of warm water which generally brought much pus mixed with some solid stool. This treatment gives much relief.

June 17: Daily stools of thin, mushy character containing pus with a couple of hard balls of fecal matter.

June 26: Occasionally no daily stools, necessitating a warm water enema. Patient is given castor oil to regulate his bowels.

July 1: *X-ray films* ("umbrathor"): After filling, the descending colon and sigmoid colon show little haustration. After emptying, the sigmoid is found to be narrow and shows only irregular coarse transverse folds. In the sigmoid and descending colon ulcer shadows are seen and the submucosa is undermined. After introducing air, the sigmoid, descending colon and renal flexure gives the picture of a braided band.

July 7: Castor oil continually causes nausea so liquid paraffin is substituted.

July 17: The stools are thin, mushy and dark brown. Macroscopically negative. Microscopically leucocytes.

*Rectoscopy* (18 cm.): Mucosa below plica recto-sigmoidale looks normal, but above this point is still somewhat red and swollen.

July 23: *Blood:* H.b. 74 Sahli; erythro. 4,475,000; leuc. 7900; differential, trans. 10½; polys. 65; small monos. 20; large monos. 4½; sedimentation after 1 hour 34 mm.

Feces rather more thick and mushy. Microscopically no leucocytes. Patient going home to continue present treatment.

*Poliklinik report:* August 4, 1933: During first few days at home there was again some blood in the stools; however, the feces soon became formed and brown in color while blood, mucus and pus were no longer observed. Sedimentation after 1 hour 30 mm.

August 17: Regular daily defecations. Feces are formed and no blood, mucus or pus could be seen. Microscopic examination negative.

*X-ray films* ("umbrathor"): After filling, the renal flexure, descending colon and sigmoid reveal fairly good haustration. Mucosa shows normal transverse foldings. The sigmoid and descending colon again reveal some longitudinal folding. Introduction of air reveals a coarse granular appearance in the renal flexure and a portion of the transverse colon.

Vaccine treatment omitted. Patient to continue with his diet. Also hydrochloric acid and pepsin.

October 20: No complaints. Patient has normal daily defecation.

*X-ray films* ("umbrathor"): Ulcers have disappeared, normal intestinal folding.

*Rectoscopy:* Normal mucosa. Sedimentation test after 1 hour 18 mm.

December 1: Condition same as October 20. Revaccinations begun. To continue for 3 weeks. Resumed his work January 15, 1934.

*X-ray films* show colon negative.

April 24, 1934: No complaints. Sedimentation test after 1 hour 16 mm.

*Final comments on vaccinations:* Success of vaccinations. In about 10 weeks subjective complaints have disappeared. Feces are then normal in consistency and contain no pathological elements. After 4½ months on the basis of X-ray, and rectoscopic examinations, we consider the intestine apparently restored to normal.

CASE 4. Mr. B. P., aged 15, farm laborer admitted to medical clinic July 22, 1933. In December, 1932, he was suddenly taken with severe diarrhea averaging 7 to 8 stools during the day and also several times at night. He felt sick and tired and had diffuse abdominal pain and cramps before each defecation. Even after his bowels moved there was often marked tenesmus. Much rumbling in abdomen. He continued to do his work but complaints up-to-date have remained about the same although rather less severe. The stools have gradually changed from watery to thin soupy and finally to a thick mushy consistency; frequency about 4 times per day. At first his distress was largely at night but lately more during the day. His appetite is good, and he knows of no special food substances which increase his distress.

*Casc notes:* The patient is long and of asthenic type. Pulse slightly arrhythmic (respiratory). Tongue normal. Papilla not atrophic. Teeth negative. Heart and lungs normal. Abdominal pressure causes rumbling. In the region of cecum, there is felt a rather smooth resistance, probably intestinal coils. The sigmoid colon can be felt as a smooth linear structure.

*Rectal examination:* Mucosa feels normal, examining finger brings no blood or mucus. Rectoscopy negative. Stools show mucus but no other pathological elements.

*Blood:* H.b. 80 Sahli; erythro. 4,840,000; leuc. 6800; eosin. 7; baso. 1; trans. 5; poly. 52; small monos. 31; large monos. 4; sedimentation after 1 hour 1½ mm.

July 28: Bowel movement sluggish, occasionally necessitating a warm water enema. Stools thick and mushy, much mucus, no blood.

*Stomach contents:* 45 minutes after test meal: H.C.L. 52; total acidity 72. Microscopically nothing remarkable. Culture for diplococcus of Bargen, negative.

August 2: *X-ray films* ("umbrathor"): On filling descending colon only slight haustration observed. Mucosa of the upper part of descending colon markedly swollen. After introducing air in sigmoid and descending colon a spotty and marbled appearance is observed.

August 5: Defecates once daily. Stools thick and mushy. Much mucus. Negative for dysentery. Positive Bargen's diplococcus.

August 10: Duodenal drainage. B-bile negative for Bargen's diplococcus. A-bile, lipase normal. Trypsin normal.

Rectoscopic examination shows no ulcers. From material obtained from the intestinal wall, cultures were made for vaccine.

August 18: Continual abdominal pain and distressing sensation in abdomen, cramps before defecations. Bowels move once or twice daily. Stools are thick and mushy containing much mucus. Autovaccinations begun.

September 7: Condition the same as August 18. Dismissed. Vaccinations to be carried out at home.

September 22: Stools thick and mushy containing much mucus.

*Blood examination:* Sedimentation after 1 hour 8 mm. H.b. 83, Sahli; leuc. 7300; eosin. 4; trans. 5; poly. 62; small monos. 24; large monos. 5.

October 28: Abdominal pain much less; feces the same as on previous examinations.

December 1: Subjective complaints are disappearing. Defecates once or twice daily. Feces thick and mushy with decrease in amount of mucus.

January 3, 1934: Practically no more complaints. Stools normal.

January 28: Patient feels that he has recovered. Stools normal and formed, containing no pathological elements.

March 11: Condition as in last report.

*Blood:* eosin. 4; trans. 4; poly. 66; small monos. 24; large monos. 2. Sedimentation after 1 hour 6 to 8 mm.

*Final comment:* After 3½ months very marked improvement observed in both subjective complaints and consistency of stools. After 5 months complete recovery.

CASE 5. Mrs. K. Z., 36, married, first admittance to the clinic February 17, 1930. During 8 months while pregnant had continuous vomiting and severe diarrhea. No abdominal pain. On January 4 was delivered of a six months dead fetus. After parturition there was some improvement, but then renewed vomiting associated with pain and rumbling in abdomen. The rumbling seemed to relieve the pain. Later, diarrhea sometimes averaging 10 movements per day of thin stools, frequently mixed with blood. Appetite good. Micturition normal.

After January 4 did not menstruate. Formerly menstruations were regular.

Most important notes: At first vomiting but not after February 20. Defecated 4 to 6 times per day, no blood. After Schmidt's test meal, stools showed many muscle fibers and much neutral fat. Forty-five minutes after test meal no free HCL.

*X-ray examination of stomach* not remarkable.

March 6: Patient was given HCL dilute and "enzypan" tablets.

March : "Pancreon" substituted for "enzypan."

March 18 to 20: Patient given an apple diet according to Moro.

March 20 to 22: General diet with limitation of fluids.

March 29: No more diarrhea. Dismissed. To continue HCL and "pancreon."

Report April 25: Occasional diarrhea. Along with medication mentioned, a generous fruit and vegetable diet prescribed.

September 2, 1931: Was readmitted. After last report developed continuous diarrhea, otherwise no complaints. About a month ago suddenly without known cause, the diarrhea became worse and severe vomiting developed.



sometimes 10 times per day. Stools often contain mucus, sometimes blood, and have disagreeable foetor. Diffuse abdominal pain in upper abdomen. Defecation not painful; loss of weight 18 Kg.

*From the notes:* Diarrhea 3 to 5 times daily. Feces bloody. Vomits about 4 times a day.

*Blood:* H.b. 80 Sahli; erythro. 5,230,000; leuc. 17,000; differential; immature cells 1; trans. 55; polys. 21; small monos. 18; large monos. 5.

October 1 to 3: HCl and pepsin plus apple diet, according to Moro. Vomiting nearly everything.

October 3: Soft diet.

October 5: Still vomiting and diarrhea. Papaverine 20 mgr. 3 times daily prescribed.

October 13: No more vomiting or diarrhea.

October 24: Papaverine discontinued.

October 30: Dismissed in good condition.

April 14, 1933: Readmitted. Four weeks ago an attack of "grippe" initiated another abdominal attack which was characterized by pain, rumbling and severe diarrhea, about 10 times daily with cramps preceding defecation. Feces watery with much mucus and blood. Frequent vomiting. Up-to-date this condition has persisted. Examination of abdomen shows no tenderness. No intestinal loops palpable.

Rectal examination not remarkable except for some mucus on examining finger.

Rectoscopy (12 cm.): Rectal mucosa thickened and bloody.

*From the notes:* Temperature up to 39° C. Nearly all food vomited. Defecations 4 to 5 times daily, feces thin, slimy and bloody with marked foetor. No neutral fat, starch or muscle fibers. Negative for dysentery but positive for Bargen's diplococcus in almost pure culture. Auto-vaccines prepared.

*X-ray (Barium Meal):* Colon shows up like stiff tube with contour as it were "eaten out." Test meal after 45 minutes: no HCl; total acidity 36; no pepsin; negative for Bargen's diplococcus.

*Blood:* H.b. 72 Sahli; erythro. 3,680,000; leuc. 8300; differential; immature cells 5; trans. 25½; polys. 47; small monos. 17½; large monos. 5. Leucocytes show toxic granulation. Red cells not remarkable. Sedimentation after 1 hour 23 mm.

April 20: Vaccine therapy begun. Was given acidol-pepsin and soft diet.

May 3: Condition improved, temperature running to 37.7° C. Defecation once a day. Feces thin, soupy with a little mucus and blood. Occasional vomiting.

May 8: Defecations once in two days. Feces formed normally. Still show blood and mucus.

May 13: General condition excellent. No more vomiting. During the past few days, defecation once in 3 days. Stools normal in form. Still some blood and mucus. Sedimentation after 1 hour 10 mm.

May 28: Temperature normal. Defecates once a day. Feces normally formed. No macroscopic blood or mucus. Microscopic mucus.

*Blood:* Trans. 9; polys. 63; small monos. 23; large monos. 5; no toxic granulation, red cells not remarkable.

June 24: No complaints. Defecates daily. Macroscopically no blood or mucus.

July 20: Microscopically feces show no pathological elements.

March 14, 1934: Feels entirely well, bowels move daily, feces normal. Sedimentation after 1 hour 4 mm.

*X-ray films ("umbrometer"):* Transverse colon shows normal haustration, remainder of the film also normal.

*Final comments on vaccinations:* After 6 weeks patient feels very well. Feces are normal in consistency and contain no pathological elements. After 11 months X-ray films appear entirely normal.

CASE 6. J. G., aged 38, married, traveling salesman; about 7 years ago, he first noticed a mucus discharge with his formed stools. At this time he developed a rather scaly condition of the skin of the extensor surface of the lower arm and the flexor surface of the right lower leg (neuro-dermatosis). There was a gradual increase in the amount of mucus excreted. Bowel movements increased to an average of twice daily and the consistency of the stools became softer. For four years has had hay fever which was relieved by treatments of pollen extract administered by Professor Benjamins.

During the last two years his intestinal condition has grown worse and the defecation frequently was preceded by a passage of mucus. Stools gradually became softer with increased frequency, averaging of late 5 to 7 daily and sometimes consisting only of mucus. Defecation was not painful neither was it preceded by any distress.

*From the notes:* A healthy looking man; mucous membranes of good color. Tongue slightly coated. Papillae not atrophic. Tonsils not enlarged. Teeth show some defects and some caries. Lungs and heart normal. Abdomen not distended. No visible peristalsis. No particular resistance to abdominal palpation. No tenderness. Parenchymatous organs not felt. Many intestinal sounds heard in the region of colon.

*Rectal examination:* Rectal mucosa feels normal. Examining finger shows no blood.

*Blood examination:* H.b. 71 Sahli; erythro. 4,100,000; leuc. 6500; differential, eos. 3; trans. 8; polys. 54; small monos. 29½; large monos. 5½. Sedimentation after 1 hour 35 mm.

November 15: *Sensitization reactions:* Cutaneous tests strongly positive for rye pollen. Defecates 3 to 4 times daily. Feces thin and mushy with shreds of mucus. Microscopically no connective tissue, no fat, no starch. Patient declares that the diarrhea is unfavorably influenced by activity.

November 20: Continued activity has resulted in more frequent defecations, from 5 to 8 times daily. Stools are thinner and there is diffuse abdominal pain but no tenesmus.

November 22: Forty-five minutes after test meal: No free HCl; total acid 16; no pepsin. Sedimentation not remarkable.

November 24: *Rectoscopy* (from 12 to 25 cm.): Mucosa bloody and swollen but no ulceration.

November 25: *X-ray film* (Barium enema): After introduction of air, a spotted and marbled appearance noted.

November 26: Given 2 cc. "campolon" twice a day; also acidol-pepsin and soft, high vitamin diet.

December 9: Defecates once daily. Stools formed but microscopically show mucus.

January 2, 1933: Instead of daily administration of "campolon" and "ventraemon," 100 grams of liver was given daily and every other day 2 cc. "campolon."

January 6, 1933: Defecates 3 to 5 times a day. Stools again thin and mushy containing much mucus, "campolon" 2 cc. twice daily and "ventraemon" 20 grains twice daily.

January 30, weak: Temperature rises daily to 38.5° C. Defecates about 8 times daily, stools are thin with mucus and blood. Patient has lost 7 kg. in last few weeks. He was given clysmata of "dermatol."

February 10: Condition serious. Daily temperature runs to 39.2° C. Defecates 10 times per day. Negative for dysentery but shows almost pure culture of Bargen's diplococcus. Vaccine prepared. Was given laudanum.

February 18: *Blood:* H.b. 46 Sahli; erythro. 3,010,000; leuc. 7300; differential; immature cells 4; trans. 28; polys. 29; small monos. 35; large monos. 4. Leucocytes show toxic granulation. Red cells not remarkable. General



condition somewhat better. Defecates 4 times per day. Thin mushy stools, much blood and mucus. Temperature up to 38 C. Autovaccinations begun.

March 2: Duodenal drainage for A-bile and B-bile. From B-bile no Bargaen's diplococci can be cultured. Normal ferments present in A-bile.

March 9: H.b. 43 Sahli; differential, eos. 2; immature cells 2; trans. 5; polys. 28; small monos. 40; large monos. 3. Slight toxic granulation. Red cells not remarkable.

March 27: General condition much improved. Defecates 3 times per day, feces thin and mushy. Macroscopically no blood or mucus. Microscopically mucus. Temperature running up to 37 C. "Ventraemon" 3 times daily 20 grams. Given "arsylen" tablets.

April 3: Has gained 3.4 kg. in past 2 weeks. Blood: H.b. 43 Sahli; differential; baso. 1; immature cells 1; trans. 14; polys. 41; small monos. 38; large monos. 5. Weight shows steady increase averaging 2 kg. a week. Temperature 37° C. Defecates twice daily, stools are formed, there is no blood or mucus. One gram of *ferrum reductum* is given 3 times a day.

May 18: Blood: H.b. 57 Sahli; sedimentation after 1 hour 21 mm. Dismissed. Vaccination therapy discontinued.

June 20: To continue with *ferrum reductum*. Defecates once or twice daily. Stools well formed, no blood or mucus.

Blood: H.b. 67 Sahli; sedimentation after 1 hour 38 mm.

July 21: General condition excellent. Blood: H.b. 76 Sahli. Sedimentation after 1 hour 8 mm.

August 20: About to resume his work.

August 28: Both knee joints markedly swollen. Free fluid demonstrable. Defecates twice a day. No blood or mucus.

September 9, 1933: Entered surgical department with very painful and swollen knee and ankle joints. Examination of joints difficult because of severe pain. The skin above the swollen areas is warmer than that over the joints. Puncture of the right knee joint brings a clear, rather opalescent, light yellow fluid which is sterile and contains mostly leucocytes. Defecates twice daily.

Stools thick and mushy, no blood or mucus.

September 23: Blood transfusion 400 cc., "campolon" 2 cc. every other day. Defecates 8 or 10 times per day. Stools thin and mushy with mucus.

October 5: Blood transfusion.

October 17: Clysmata of "rivanol" 1 to 1000. Defecates 7 times a day.

October 26: Irrigations discontinued. Defecates 13 times a day. Stools thin and mushy with mucus and blood. Referred to medical department.

October 30: Readmitted to medical department. Temperature 38.5° C. General condition poor. Defecates 25 times a day, stools consist of thin, slimy, bloody material. Weight 56 kg. (May 18, 72 kg.). Temperature 38.6° C.

Therapy: Takes only a couple of zwiebach and fluid in the form of weak tea. Laudanum and acidol-pepsin given.

Blood: H.b. 52 Sahli; erythro. 3,620,000; leuc. 6500; differential; baso. 1; eos. 1; trans. 12; polys. 29; small monos. 45; large monos. 12. Sedimentation after 1 hour 35 mm.

November 3: Defecates 15 times daily. Stools contain slimy bloody material, also Bargaen's diplococcus. Dysentery negative. Tubercle bacilli negative.

Diet: Toasted bread, soup, zwiebach, potato puree, banana, orange juice.

Rectoscopy: (12 cm.): Mucosa bloody and swollen.

November 12: Temperature 37.8° C. Autovaccines begun. Laudanum dosage gradually decreased. Given "idosan." Knee joints now only slightly tender on palpation.

December 12: Rectoscopy (15 cm.): Mucosa bloody and swollen.

X-ray films ("umbrathor"): Colon shows nodular hyperplastic stage of ulcerative colitis.

September 16: Blood: H.b. 55 Sahli. *Ferrum reductum* 3 grams daily. Feces show no blood or mucus macroscopically. Weight 60 kg.

December 31: Defecates 6 times daily, feces thin and mushy, no blood or mucus.

Blood: H.b. 75 Sahli.

February 22: Knee joints normal.

X-ray films ("umbrathor"): Nodular stage of ulcerative colitis or pseudopolypsis (?). Vaccination discontinued. Direct sunlight advised.

April 10: Patient feels that he has recovered. Light work allowed on his urgent request. Defecates twice daily. Stools normally formed, no pathological elements. Sedimentation after 1 hour 20 mm.

Final comments on vaccinations: After 10 weeks all subjective symptoms have disappeared and no more pathological elements found in stools. A few months later an acute arthritis developed. Most likely psychic factors were instrumental in causing an acute exacerbation of colitis. Revaccination brings recovery.

CASE 7. N. N., aged 30, high school teacher, married. In the summer of 1926 he first noticed blood in the stool and tenesmus. Rectoscopy revealed ulcers in the sigmoid colon. Enemas of silver nitrate solution brought improvement.

March 22, 1927: Admitted to the medical clinic. Maximum temperature 37.3° C. Stools negative for dysentery. Negative for tubercle bacilli. Treatment 30 mgr. of emetine daily, subcutaneously.

April 11: Emetine discontinued. Is getting clysmata of silver nitrate solution 2%.

April 28: Silver nitrate discontinued and  $\frac{1}{2}$  "dermatol" irrigations substituted.

May 2: "Trannalbin" 0.5 grams twice daily.

June 27: Clysmata of "dermatol" and "tannalbin" discontinued. Was given bacteriophage 1 cc. every 5 days. Cleansing enema in the morning.

July 13: Last dose of bacteriophage given. Last injection caused no temperature rise.

July 23: Stools thick and mushy, occasionally blood and mucus. Dismissed. Soon after dismissal there was more frequency of defecation with thin, bloody mucus stools.

August 28: Defecated 5 times a day. Much blood. Temperature up to 40° C.

September 28, 1928: Readmitted to medical clinic at Groningen. X-ray of descending colon shows pseudo-polypsis. Blood: Leuc. 6900; differential, eos. 3; trans. 19; polys. 36; small monos. 36; large monos. 6. Clysmata of tannin solution. Low residue diet. Later fresh vegetables.

January 7, 1929: Tannalbin 3 times daily 0.5 grams.

January 16, 1929: Rectoscopy: Mucosa atrophic. "Dermatol" clysmata. Blood gradually disappearing from feces although these remain frequent and thin. Resumed his occupation in May. After a few days, stools again become bloody.

May 10, 1929: Readmitted to medical clinic. Diet: bananas, oranges, figs, grapes and yogurt.

May 16: Clysmata of 3% hydrogen peroxide and tannalbin solution.

May 19: Clysmata discontinued: Given 50 grams of liver per day, also raw vegetables, direct sunlight and *bolus alba*. Defecates 5 to 8 times daily, much blood and mucus. Temperature up to 38.5° C. Clysmata of 300 cc. water containing 2 cc. adrenalin and 1% yaten.

May 31, 1929: Because of poor condition, transferred to surgical division.

June 7: Rectoscopy: Severe inflammatory condition. Polyp removed.

June 13: Appendicostomy: Irrigations with camomile tea. Kelling's diet.

June 27: Feels much better, much less pain but still blood and mucus.

July 10: Defecates once or twice daily. Returned to medical department. Much blood and mucus in the stools. Irrigations of camomile tea discontinued and clysmata of "rivanol," tannin and "dermatol" substituted. Change in medication always seems to bring about slight improvement which, however, is not permanent. The patient seems to feel that his psychic attitude has a great influence on his intestinal condition.

August 30: Condition improved to such extent that he is able to resume his work. Again recurrence of blood in two weeks and condition gradually growing worse.

September 14: Marked proctitis. Rectal wall inflamed with purulent material attached to mucosa for a distance of 22 cm. Bargaen's diplococcus not found.

September 21: Diplococcus present. Vaccine prepared.

September 28: Autovaccinations begun. This treatment resulted in improvement.

March 21, 1931: Feels exceedingly well. Blood: H.b. 72 Sahli. Rectoscopy shows no abnormalities. Defecates once daily. Feces formed, no mucus or blood.

June 31: Again vaccinated, 10 injections given.

April 5, 1933: Was asked to come for examination. Patient has done his work for 2½ years without any complaints. No abnormal symptoms. Feces are thick and formed in part. Microscopically no pathological elements.

May of 1933: Sudden exacerbation of 10 defecations daily with tenesmus. Stools slimy and bloody, Bargaen's diplococcus found. Autovaccinations for 8 weeks results in gradual recovery. Patient, however, went back to work too soon and his condition again becomes worse.

January 24, 1934: Readmitted to medical clinic. The sigmoid colon can be felt as a linear tube which is painful to palpation. Rectal examination: Mucosa feels rough and examining finger shows blood and mucus.

*Rectoscopy:* Mucous membrane swollen. Defecates 5 to 8 times daily. Feces show blood and moderate amount of mucus. Negative for dysentery. Positive for Bargaen's diplococcus. At first the treatment consisted only in the use of a diet poor in residue and magnesium sulphate in the morning because of a continuous obstipation.

*Blood:* H.b. 75 Sahli; erythro. 5,100,000; leuc. 6800; differential; eos. 2; trans. 7; polys. 44; small monos. 43; large monos. 4. Sedimentation after 1 hour 10 mm. Wassermann negative. Forty-five minutes after test meal: Free acid 31; total acid 60; no diplococci in stomach contents.

February 9: Condition somewhat easier. Defecates two to three times a day. Stools thick and mushy, some portions consisting of blood and mucus.

*X-ray films* ("umbrathor"): Descending colon reveals pseudo-polyposis. Remainder of gut gives a normal shadow.

February 20: General condition as of February 9: *Blood:* Differential eos. 2; trans. 3; polys. 44; small monos. 48; large monos. 3. Sedimentation after 1 hour 8 mm. Autovaccinations begun.

March 20: Defecates once daily. Stools sometimes normal, sometimes thick and mushy. No blood or mucus.

March 30: Dismissal. No complaints. Vaccinations discontinued. Is to remain at rest for some time.

April 25: No complaints. Defecates once daily. Stools sometimes mushy, sometimes formed. No blood or mucus.

*Final comments on vaccinations:* In this extreme case in which pseudopolyposis had developed, complete clinical cure followed autovaccinations. Nevertheless, after 2½ years there was a recurrence which again was followed by recovery after autovaccination. The final results in this case, however, cannot be definitely foretold.

CASE 8. K. Z., a seaman, aged 64, married, admitted April 27, 1932, to the surgical clinic. For about 10 years for periods of several months had much blood and mucus in the stools but at intervals these again were normal. Four weeks before admission patient developed sudden diarrhea, about 6 times daily. Feces containing blood and mucus. Tenesmus. Feels tired and very much exhausted.

*From the notes:* Gives the impression of being healthy. Mucous membrane pale. Teeth carious and defective. Heart and lungs normal.

*Abdominal examination:* In the lower left quadrant the sigmoid colon can be felt like a band; otherwise nothing remarkable.

*Rectoscopy:* (22 cm.): Mucosa hyperemic with small hemorrhagic areas, but no ulcers. Feces contain much blood.

*Blood:* H.b. 50 Sahli; erythro. 3,830,000; leuc. 7800. Was given clysmata of rivanol 1 to 5000 twice daily.

May 23 and June 12 blood transfusions.

July 8: *Rectoscopy:* Mucosa bloody. Was dismissed. Family physician to continue administrations of "rivanol" clysmata.

Report October 7: Few complaints. Given daily clysmata of "rivanol" solution.

Report November 4: Condition much improved, clysmata discontinued.

March 8, 1933: Some red blood in the stools. Sent to medical department for vaccine therapy.

March 13, 1933: Medical department Poliklinik. Not so well of late. Complains particularly about stiffness in the joints. More blood in the stools than formerly. In the lower left quadrant a loop of the sigmoid colon can be felt, tender to palpation. Digital examination of rectum negative.

*Rectoscopy:* (22 cm.): Mucosa hyperemic and swollen. Stools thick and mushy and contain much bloody mucus, has disagreeable foetor. Negative for dysentery. Positive for Bargaen's diplococcus. Vaccines to be made.

*Blood:* H.b. 48 Sahli; erythro. 4,110,000; leuc. 4800; differential, eos. 1; trans. 5; polys. 53; small monos. 34; large monos. 7. Sedimentation after 1 hour 15 mm. Stomach lavage not successful.

March 21: Forty-five minutes after test meal no free acid; total acid 28; pepsin present. Vaccine therapy begun. General diet, but coarse foods forbidden. Given HCL.

April 25: Less tired. Joint pains have disappeared. Less blood and mucus in the stools.

*Blood:* H.b. 50 Sahli.

May 26: Feels better than he has for two years. Defecates every other day, occasionally a semi-solid stool some parts of which contain blood and mucus. Sedimentation after 1 hour 19 mm. *Blood:* H.b. 50 Sahli.

June 30: *Blood:* H.b. 50 Sahli. Feces as on May 26. Vaccinations discontinued.

August 15: *Blood:* H.b. 52 Sahli. Feces as before.

Early in October was admitted to clinic a few days for observation. No subjective complaints. Has daily stool, semi-solid with some blood.

*Rectoscopy:* (22 cm.): Polyposis. Hyperemic mucosa. *X-ray films* ("umbrathor"): Polyposis of descending colon. *Blood:* H.b. 52 Sahli. Again vaccine therapy for a few weeks.

March 10, 1934: Condition unchanged. *Blood:* H.b. 52 Sahli. *Ferrum reductum* one gram 3 times daily. Again vaccination therapy for a few weeks.

May 7: General condition shows no change.

*Rectoscopy:* (23 cm.): Polyps. Mucosa slightly hyperemic. *Blood:* H.b. 60 Sahli; differential; eos. 1; trans. 3; polys. 58; small monos. 35; large monos. 3. Sedimentation after 1 hour 12 mm. Feces thick and mushy with occasional blood.

*Final comments on vaccinations:* In this rather advanced case in which pseudo-polyposis developed, vaccination therapy brings a measure of improvement in general condition.

CASE 9. Mr. S. de L., aged 29, cattle dealer, single. For the past year has noticed blood in his stools, defecations more frequent than normal. For two weeks has been acutely ill with severe diarrhea, the stools often consisting largely of blood. Before defecation and sometimes for about 10 minutes after, there is tenesmus.

*From the notes:* Gives the impression of being ill. Pulse and respiration normal. Mucous membrane good color, teeth show some defects otherwise are well taken care of. Has 3 artificial upper incisors. Tonsils normal. Abdomen flat. Normal tympany. Liver palpable just below the ribs. Slight tenderness in lower left quadrant. No intestinal loops can be felt.

*Rectal examination:* Mucosa feels thickened, examining finger shows blood.

*Rectoscopy:* (22 cm.): Rectal mucosa edematous and bloody. Material removed from rectal wall is negative for diplococci of Bagen.

September 4: Urine positive for urobilin and acetone.

September 7: Patient feels ill. Temperature up to 38.6° C. Defecates 8 times daily. Feces show blood and mucus. Has abdominal pain and tenesmus.

*Blood:* H.b. 78 Sahli; erythro. 5,110,000; leuc. 11,200; differential, immature cells 3; trans. 22; polys. 48; small monos. 20; large monos. 7. Sedimentation after 1 hour 42 mm. Forty-five minutes after test meal, no free HCL; total acid 30; pepsin present. Microscopically nothing remarkable. Stomach contents show no Bagen's diplococci. Is given soft, high vitamin diet and dilute HCL.

September 11: *X-ray films* ("umbrathor"): After filling, the transverse and descending colon appear like a stiff tube. Contours look irregular and saw-toothed. Enema reaches small bowel. Mucosa of the ascending colon and the right part of transverse colon reveal coarse foldings. The distal part of transverse colon and descending colon look like a stiff honeycombed structure. After introduction of air both transverse and descending colon remain narrow and give a marbled appearance.

September 13: Temperature still running up to 38.6° C. Defecates 10 times a day, much blood and mucus. Repeated examining for dysentery and Bagen's diplococcus negative. Second rectoscopic examination: Material from rectal wall shows Bagen's diplococcus. Vaccine prepared.

September 16: *Sensitization tests:* (Storm van Leeuwen): These are all negative.

September 25: Temperature running up to 37.5° C. Defecates 6 times a day. Still much mucus and blood. Vaccine therapy begun.

October 18: Stools thick and mushy, occasional stool shows no macroscopic blood or mucus.

October 30: One or two stools daily. Well formed. Still microscopic mucus.

November 5: Dismissed. To continue the same treatment.

December 15: No subjective complaints. Defecates once a day. Stools normally formed, and contain no pathological elements.

*Blood:* H.b. 78 Sahli; erythro. 4,600,000; leuc. 9200; differential, baso. 1; trans. 3; polys. 57; small monos. 31; large monos. 8. Sedimentation after 1 hour 6 mm.

*X-ray films* ("umbrathor"): Descending and transverse colon show no haustration. Otherwise fairly normal. Loops of small bowel can be felt. Mucosa of transverse and descending colon still show honeycombed appearance. Vaccination discontinued.

February 16: No complaints. Stools normal. Patient not allowed to work.

May 4: No complaints. Has daily stools normally formed, no blood, no mucus.

*X-ray films* ("umbrathor"): Films show normal haustration. Ascending colon shows normal folding, transverse colon still somewhat spastic. Normal folds again beginning to appear in descending colon. Injection of air reveals nothing remarkable.

*Blood:* H.b. 70 Sahli; differential, eos. 1; trans. 4; polys. 59; small monos. 30; large monos. 6. Sedimentation after 1 hour 16 mm. Light work permitted. Was revaccinated for 2 or 3 weeks.

*Final comments on vaccination:* After 5 weeks, clinical symptoms disappeared. After 10 weeks stools show no more pathological elements. After 7 months Roentgen rays reveal only slight departures from the normal.

CASE 10. Mrs. S. V. D. L., aged 53. Was treated in 1925 in the medical clinic for bronchiectasis. Pneumothorax treatments gave improvement. Was first admitted for abdominal complaints March 11, 1930. Had then been troubled for a year with continuous pain in the lower left quadrant. This was more intense just before defecation. Bowels moved rather sluggishly and she generally needed laxatives. No diarrhea. Some blood in the stools during past few weeks.

*From the notes:* There is marked tenderness in the lower left quadrant. The sigmoid colon is palpable. In the mid-line below the navel a painful smooth mass can be felt.

*Rectoscopy:* (15 cm.): No abnormalities seen.

*X-ray films* of stomach and follow-up films of the bowel show no departures from normal.

April 5: Stools thick, mushy. Macroscopically, blood and mucus.

April 12: Forty-five minutes after test meal; no free HCL; pepsin present. No lactic acid. Was given dilute HCL. During her stay here, there was continual complaint of pain in the lower left quadrant.

May 17: Dismissed. To wear an abdominal binder.

September 18, 1931: Report: Still has abdominal pain and tenderness in the lower left quadrant.

August 11, 1933: Readmitted because of persistent abdominal pain in the lower left quadrant. Worse before defecation.

*From the notes:* Pulse normal. Teeth have many defects, some caries. Tongue—papillae not atrophic. Tonsils not enlarged. Trachea slightly deflected to the right. Over the lungs marked evidence of old bronchiectasis on auscultation. Heart slightly dilated to the left. Spleen palpable. In the left iliac fossa a tender band about the thickness of one inch can be felt from above downward.

*Recto-vaginal examination:* Uterus ante-flexed. Rectal mucosa feels thickened, examining finger shows mucus.

*Rectoscopy:* Rectal mucosa looks normal; however, some bloody mucus can be removed with a gauze applicator. This is positive for diplococcus of Bagen. Vaccine prepared.

August 17: Defecates every other day, occasionally a small glycerine enema needed. Feces show hard particles with much bloody mucus, some pus. Microscopic mucus, red cells and leucocytes. Negative for dysentery, positive for Bagen's diplococcus. Forty-five minutes after test meal; free HCL absent, pepsin present. No Bagen's diplococci in the stomach contents.

August 18: *X-ray films* ("umbrathor"): Film shows normal haustration. Contour normal. The enema reaches small gut. Injection of air reveals ulcers in descending colon and sigmoid colon.

*Blood:* H.b. 74 Sahli; erythro. 5,000,000; leuc. 8000; differential, eos. 1; trans. 4; polys. 49; small monos. 40; large monos. 5. Sedimentation after 1 hour 28 mm.

August 30: Autovaccinations begun. Given HCl dilute and cascara. General diet containing no coarse food substances.

September 22: Defecates daily. Takes cascara regularly. Feces thick and mushy with bloody mucus and pus. Still having abdominal pain. Was dismissed to his home to continue treatment.

October 20: Report: Abdominal pain much better. Feels much brighter. Feces thick, mushy and contain mucus.

November 15: Only occasional slight pains in the abdomen. Feces normally formed and contain no pathological substances. Vaccinations discontinued.

December 10: No more pain. Sigmoid colon still slightly painful on pressure.

*Blood:* Sedimentation after 1 hour 12 mm.

February 26, 1934: No complaints. Revaccinated for a couple of weeks.

April, 1934: No complaints. X-ray examination refused.

*Final comments on vaccination:* After 14 weeks all complaints have disappeared, and stools no longer contain any pathological elements.

CASE 11. Mr. J. H., laborer, aged 21, married, admitted to medical clinic November 27, 1933. For the past three months had mucus and blood in the stools. Defecates daily. This is followed for some little time by tenesmus. From time to time sharp pain in the lower left quadrant. Frequently feels very much fatigued. There are no similar cases in this patient's community.

*Physical examination:* Appears healthy. Pulse normal. Teeth, no caries. No defects. Has pyorrhea. Tonsils not enlarged. Heart and lungs normal.

*Abdomen:* Except for some tenderness in the region of descending and sigmoid colon examination nothing remarkable.

*Rectal examination:* Mucosa feels normal, examining finger brings some blood.

*Rectoscopy:* No abnormalities.

*From the notes:* Defecates daily which is followed by some urge. Feces show blood and mucus, much odor. Negative for dysentery, positive for Bargen's diplococcus. Vaccine prepared.

*Blood:* H.b. 63 Sahli; erythro. 5,200,000; leuc. 8200; differential, eos. 2; trans. 3; polys. 48; small monos. 37; large monos. 10. Sedimentation after 1 hour 8 mm. Wassermann negative. Was given *ferrum reductum*, 4 grams daily. Forty-five minutes following test meal; free acid 20; total acid 42.

*X-ray films of colon ("umbrathor"):* The lower part of descending colon and the upper part of sigmoid look tube-like. No intestinal folding observed.

December 18: Vaccine therapy begun. Given a subcutaneous injection every 3 days. Diet, low residue and vitamin rich.

January 9, 1934: Doses 0.1; 0.2; 0.4 cc. vaccine do not cause any rise in temperature, but doses larger than 0.8 cc. bring about a rise up to 39° C. The following dose is then decreased to 0.6 cc. Later the dosage can be gradually increased to 1.2 cc. without any serious temperature rise.

January 23: Defecates daily. Mucus and blood in stools.

*Blood:* H.b. 78 Sahli; reduced iron discontinued.

February 16: Inasmuch as vaccine therapy has produced very little change another culture was isolated from fresh pathological material. New vaccine was then given subcutaneously.

March 6: Stools contain less blood and mucus.

March 16: No more abdominal pain but still some painful tenesmus. Defecates daily. Stools show occasional blood. Vaccinations discontinued. Dismissed. To continue his diet. For the present not allowed to work.

*Final comments on vaccinations:* Vaccination in this case brought very little recovery in 8 weeks. Fresh vaccine, however, resulted in marked improvement in 4 weeks.

CASE 12. Mr. H. Van D. W., 32 years old, farmer, admitted February 16, 1933, to medical clinic. In his 15th year he began to develop a diarrhea, his bowels sometimes moving every hour. At intervals this was less frequent. The stools were watery or thin and mushy containing blood and mucus. After this condition had existed for 2 years patient consulted a specialist who treated him with elysmata and medicines by mouth. A year later the condition was improved to such a degree that rectal medication was discontinued. Had no complaints up to the winter of 1933. At that time, for a couple of days he developed severe diarrhea with watery stools containing mucus and blood. After a few days the frequency diminished to 2 or 3 times a day the stools still containing blood and mucus. Patient felt very tired and had marked distress and a great deal of rumbling in the abdomen which has steadily persisted to date. Generally the stools are thin and mushy but occasionally for a couple of days thick, but all regularly contain blood and mucus. There is no tenesmus. Whenever he comes in contact with corn and also when going to bed (feather-bed) he develops a paroxysm of coughing with a watery nasal discharge, (*rhinitis vasomotoria*).

*Examination:* The patient looks fatigued. Pulse normal. Tongue shows normal papillae. Has one defective tooth. Tonsils normal. Heart and lungs normal. There is slight tenderness to palpation in the region of descending colon. No intestinal loops can be felt. Has rhagades in anal region.

*Rectal examination:* Mucosa normal. Examining finger shows no blood or mucus.

*Rectoscopy:* Negative. Mucosa normal.

*From the notes:* Feces thick and mushy, much mucus and blood, odor. Defecates once or twice daily. No undigested food substances. Negative for dysentery. Bargen's diplococcus positive. Vaccine prepared.

*Blood:* H.b. 75 Sahli; erythro. 4,500,000; leuc. 7900; differential, eos. 2; trans. 4; polys. 65; small monos. 21; large monos. 5. Sedimentation after 1 hour 16 mm.

*Sensitization tests* (Storm van Leeuwen) cutaneous, weakly positive for fish. Intracutaneous for mites and moulds. Forty-five minutes after test meal; no free HCl, no pepsin. Microscopically nothing remarkable.

Stomach contents negative for Bargen's diplococcus. Duodenal drainage. A-Bile, trypsin and lipase normal. Culture for gram-positive diplococci in B-Bile negative.

*X-ray of colon* (barium enema): After filling, sigmoid colon shows no haustration. Contour finely saw-toothed. After injection of air the ascending, transverse, descending and sigmoid colon present a spotted and marbled appearance. The transverse colon at the hepatic flexure gives the picture of a braided band.

April 10: Vaccine therapy begun. Defective tooth extracted. Given HCl and pepsin. No coarse food substances allowed.

May 3: Much improvement. No more abdominal complaints. No more fatigue. Is able to do his work. Defecations and stools as in the beginning of treatment.

June 7: Feels well, has a daily morning defecation. Stools normally formed. Still microscopic mucus. Complaints about his anal condition, (rhagades).

July 28: No complaints. Feces normal, no pathological substances present. Vaccine therapy discontinued.

September 9: No complaints. *X-ray films:* Enema reaches the small bowel. In the transverse colon at the hepatic flexure there are no normal transverse folds. The structure as a whole has the appearance of a sponge.

January 15, 1934: Sudden diarrhea twice daily, (a little son developed diarrhea also). Stools thin and mushy

containing mucus. Much abdominal distress. Bargen's diplococci present in the stools.

February 1: Revaccinations begun.

March 26: There has been gradual improvement. Stools normally formed. Vaccinations discontinued.

*X-ray films:* The transverse colon at hepatic flexure now shows normal intestinal fold.

May 14: No complaints. Defecates once a day, sometimes twice daily. Stools normal. Sedimentation after 1 hour 3 mm.

*Final comments on vaccinations:* In this case 3 months after vaccination therapy was begun, the clinical symptoms disappeared. X-ray, however, revealed marked departures from the normal. After 6 months, mucus again appeared in the stools. Revaccination resulted in recovery and the X-ray picture again became entirely normal.

CASE 13. The patient, Doctor S., of Leeuwarden, had been ill for 8 years with long intervals of comparatively good health. Has diarrhea and tenesmus. Stools soft but fairly well formed; contain mucus. In the region of sigmoid colon one can feel intestinal loops which are tender to palpation.

*Rectoscopy:* Marked injection of rectal mucosa. The patient has been on a dietetic regime and treated with clysmata. This treatment proved mildly successful. Vaccination therapy brought about gradual improvement.

CASE 14. The patient, Doctor H., of Assen, had been ill 1 year with diarrhea and tenesmus. Thin mushy stools. Transverse and descending colon palpable and tender on pressure.

*Rectoscopic examination negative:* Stomach contents: No free HCl. Before vaccination treatment was begun, clysmata of "dermatol" had been used without success. Along with vaccination therapy HCl was administered. This treatment resulted in complete recovery.

CASE 15. The patient, Doctor H. P. M., of Groningen, has for the past 4 months had serious symptoms; prior to that time had had some rather indefinite complaints. Generally obstipated. Feces contain mucus and blood. Palpation painful in region of cecum and sigmoid colon.

*Rectoscopy:* Mucosa injected and ulcerated.

*X-ray films of colon:* (Doctor Keyser) Diagnosis: Typical colitis ulcerosa.

*Fractional examination:* Stomach contents: 0/25; 20/40; 25/42; 15/38. No other therapy resorted to before vaccination treatment was begun. Was given soft diet and eventually mild laxatives. Vaccination therapy resulted in complete recovery.

CASE 16. The patient, Doctor v. B., of Tilburg, had been ill 6 months with diarrhea, tenesmus and liquid stools of mucus, blood and pus. Transverse and descending colon are felt and are tender to palpation.

*Rectoscopy:* Mucosa inflamed.

*X-ray films:* Marked departures from the normal in transverse and descending colon. Before vaccination therapy was begun, patient had been on a dietetic regime and had been treated with clysmata. Was given a vitamin rich, low residue diet. Two months after vaccination was begun, there was improvement which still continues. Feces now formed and contain no mucus, blood or pus.

## REMARKS

In order to eliminate the possibility of dysenteric infections, all stools were examined for amoebic and bacillary dysentery. Agglutination reactions according to Flexner, Strong and "Y" were also made on the blood of all patients. These were consistently negative. X-ray films of the colon were taken after the introduction of a contrast mass clysmata.

Results in the 16 patients treated are as follows:

8 completely cured. No. 3 is now symptom free after 10 months. 6 (1 with pseudo-polyposis) show marked

improvement. 2 (1 with pseudo-polyposis) show moderate improvement.

## CHARACTERISTICS OF DIPLOCOCCUS; ISOLATION AND CULTURE METHODS

Bargen describes the organisms found in cases of ulcerative colitis as plump, lancet formed, gram-positive diplococci often growing in pairs and fours. Microphologically they very much resemble pneumococci having a capsule and also having the property of forming short chains in fluid media.

As far as the choice of media is concerned, it may be observed that, as a rule, they grow very well in agar and bouillon. They are, however, semi-anaerobic. Sugar favors the growth very remarkably, therefore, the use of 2% glucose-agar or bouillon is quite general.

Growth is particularly good on blood-agar. Surrounding the colonies grown on this media, we see a hemolytic zone surrounded by a greenish zone. On agar, the colonies are small, round, slightly elevated, grayish and dry and, in some respects, resemble those of streptococcus but differing from those of enterococcus. They differ further from cultures of enterococcus in that they do not grow on gelatin and do not coagulate milk which enterococcus does. Again in contrast with the most common streptococci, diplococci cloud bouillon and give rise to sediment. Diplococci also differ from streptococci and pneumococci in their greater resistance to heat and also in the fact that they are not dissolved in bile but grow very well in this medium. Their growth in Muller's medium and their thermo-resistance we shall mention later. Soon after isolation the diplococci ferment dextrose, lactose, saccharose, maltose, raffinose, salicin, and sour milk. Later these fermentation properties may vary, particularly, in regard to the last six substances mentioned. Diplococci do not ordinarily ferment mannite while the *streptococcus faecalis* does. They differ from the pneumococci in that they do not ferment inulin.

AN ESSENTIAL FOR PROPER IDENTIFICATION IS THE AGGLUTINATION REACTION: Bargen developed agglutination sera with high titers in rabbits which was 10 times greater than that of enterococci. Agglutination with the serum of patients has, according to Bargen, very little differential-diagnostic value, inasmuch as agglutinins are present in only very small quantities. In connection with the differentiation from pneumococci it must be noted that the agglutinating pneumococcus sera of types 1, 2, 3 do not agglutinate these diplococci.

Sensitivity of experimental animals we shall discuss in the section on animal experimentation.

Bargen believes that the portal of entry of the diplococcus is the oral cavity. He finds support for this belief in the observation that frequently they are present in periapical tooth abscesses and in abscessed tonsils.

Differing from the original method which Bargen employed for the isolation of the diplococcus, he advises in his later publications the following method: Material for the cultures should be obtained by rectoscopy. Before this is carried out the bowel should be thoroughly cleansed with castor oil given the evening before, and a couple of warm water enemas in the morning. As far as possible aseptic precautions should prevail. Cotton swabs are brought in intimate contact with the base of ulcers or with the bleeding mucosa. Each swab is immediately placed in warm dextrose brain broth and then put in the incubator for 6 hours. One set of 3 additional tubes of dextrose brain broth is now inoculated with material from each of the two original tubes by shaking the swab into all tubes of each of the sets of three so we now have 3 new cultures of each original 6-hour growth. One set of 3 tubes is heated for 45 minutes at 55 C and placed in the incubator. The other set is incubated immediately. After 18 hours gram-stain preparations are made of the cultures.



From the tube in which the most gram-positive diplococci are found, blood agar preparations are made as follows:

One drop of the tube culture is mixed with 10 cc. of physiological salt solution and one drop of this mixture placed in 10 cc. of blood agar. From this blood agar, later a plate is made. Similar plates are made with several dilutions of the material from the selected tube of blood agar. All these plates are incubated over night. Examination then shows colonies of diplococci surrounded by a greenish zone. Between this zone and the colony there is a hemolytic zone. To isolate a pure culture, material from these plates is again placed in dextrose brain broth for 18 hours at 37° C.

Bargen does not find the organism in cultures of feces but they are frequently present in large numbers in cultures from pus, mucus or blood mixed in the stool.

Buttiau and Sevin, Rafsky and Manheim, Gutierrez, Lastra and Blanco all used Bargen's technique for isolation and culture of the germs. Fradkin and Gray also isolated the diplococcus from material taken from the rectal wall through the rectoscope. This was not always successful at the first attempt and sometimes needed to be repeated. The material they gathered was immediately put in warm dextrose bouillon and placed for 6 hours in the incubator. If gram-positive diplococci were found they made a second culture in dextrose bouillon. If after 12 hours the diplococci were present in this culture, plates of blood agar were made and in 18 to 24 hours the characteristic small, round, slightly elevated, grayish, rather dry colonies of the diplococcus appears. In some cases the cocci have been isolated from the muco-purulent bloody material found in the feces.

*Isolation and culture methods used by the Author:* The rather elaborate isolation method used by Bargen and the difficulties involved in his technique are probably the reasons that many investigators were not successful in isolating the diplococcus of *colitis ulcerosa*. In our work we followed the method of Van der Zoo de Jong whose technique is somewhat similar. In order to eliminate the associated intestinal organisms, he made use of the following cultural characteristics:

(1) As a rule the diplococci can withstand a temperature of 57° to 58° C. for an hour very well. In this they differ from many other bacteria.

(2) While many intestinal organisms grow feebly or not at all in Müller's fluid, the diplococcus grows very well in this medium.\*

*The following materials were used for growing the diplococci:*

(1) Culture tubes with Müller's fluid (not more than a week old).

(2) Tubes of about 10 cc. capacity of heavy glass filled about 2/3 full of 2% glucose bouillon and closed with rubber stoppers. These were especially used for heating.

(3) Culture tubes with 2% glucose bouillon with cotton stoppers.

(4) Culture tubes with well shaken 2% solutions of glucose agar for making plates.

Material for culture obtained by the method of Bargen is now placed in two tubes with Muller's medium, relatively a larger quantity in one tube than in the other.

\*Tetrathionate Bouillon: Four and one-half grams of dry sterilized chalk is mixed in 90 cc. of Bouillon. To this is added 10 cc. of 50% Sodium Hyposulphite Solution (sterilized in live steam) and 2 cc. of the following formula: Iodine 25, Potassium Iodid 20, Aq. Dest. ad 100.

TABLE I

*Bargen's diplococcus was suspended in stomach contents containing no HCL. After incubating for 3 hours, glucose bouillon cultures of the suspension were kept at 37° C. As the following table shows, the bacteria remained alive in almost every instance*

| Name | Free HCL | Total Acidity | Pepsin     | Lactic Acid | Living Bacteria |
|------|----------|---------------|------------|-------------|-----------------|
| B    | 0        | 27            | +          | —           | +               |
| V    | 0        | 26            | +          | —           | +               |
| S    | 0        | 32            | +          | —           | —               |
| D    | 0        | 30            | negligible | —           | +               |
| J    | 0        | 36            | —          | —           | —               |
| P    | 0        | 5             | trace +    | —           | +               |
| V    | 0        | —             | +          | —           | +               |
| K    | 0        | 38            | +          | —           | +               |
| H    | 0        | 6             | +          | —           | +               |
| P    | 0        | 57            | —          | —           | +               |
| R    | 0        | 12            | +          | trace +     | +               |
| d.V  | 0        | 44            | +          | —           | —               |
| B    | 0        | 20            | +          | +           | +               |
| R    | 0        | 14            | —          | —           | +               |

These are then incubated at 37° C. Also two of the stoppered tubes with glucose bouillon are inoculated, again a larger quantity in one than in the other. These are placed in a water bath at about 57° C. and kept at a temperature of 57° to 58° C. for 1 hour. Inoculations from these tubes are then placed in glucose bouillon and from the tube containing the largest amount of material to be cultured, glucose agar plates are also made. At this point all the tubes (including those which have been heated) and the plates are placed in the incubator. On the following day, the presence or absence of diplococci is demonstrated by making gram preparations of all cultures. If no diplococci are found in the heated material, new cultures are again made. Glucose bouillon preparations and glucose agar plates are now made of the tubes containing Muller's medium.

Frequently after the heating and also after the incubating in Muller's medium, diplococci are often present in pure culture. In some cases in which no pure culture can be obtained from Muller's tubes, it is very often possible to get one by introducing a few drops of Muller's solution in glucose bouillon and then carrying out the heating process. The possibility also remains of inoculating Muller's solution with material which has been heated.

One does not consider the result negative until after the cultures examined have been incubated for 48 hours. The more detailed identification of the isolated cocci has already been discussed. If the characteristics of the organisms are those of Bargen's *diplo-streptococcus*, the preparation of vaccine is then undertaken. This should contain about 2 billion bacteria per cubic centimeter.

If isolation of diplococci from mucus, blood or pus in the feces is attempted, it must be remembered that often times fecal material contains organisms which in many respects resemble those of Bargen.

We examined the feces for the diplococcus of Bargen in 12 individuals with no abdominal complaints.

1 case was positive

2 cases in which material was taken from the base of tuberculous ulcers in the colon at autopsy, were negative

2 cases in which material was taken from base of typhoid ulcers at autopsy were negative

One case in which material was taken from the base of a carcinomatous ulcer of the rectum was negative

Feces of 6 patients with rectal carcinoma gave the following results: B-Coli, positive in 2 cases



## Results of Auto-Vaccinations

| Condition when vaccine therapy was begun |                   |                                    |                     |                                    |                                                                                                                                                                                                                           |
|------------------------------------------|-------------------|------------------------------------|---------------------|------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Name                                     | Length of Illness | Stools, Feces                      | Rectoscopy          | Röntgenology                       | Course                                                                                                                                                                                                                    |
| 1. M.                                    | 1 year            | 4 daily, thin, mushy, blood, mucus | bloody, swollen     | descending colon                   | After 9 weeks clinical symptoms cleared up. Four months later more complaints, most likely the results of insufficient after treatment.                                                                                   |
| 2. B.                                    | 6 mos.            | 4 daily, thin, mushy, much mucus   |                     | descending colon, hepatic flexure  | Disappearance of all clinical symptoms after 12 weeks.                                                                                                                                                                    |
| 3. P.                                    | 4 years           | 2 daily, mucus, blood, pus         | bloody, swollen     | sigmoid colon                      | Disappearance of all clinical symptoms after 10 weeks. Four and one-half months later rectoscopy and X-ray examinations are negative.                                                                                     |
| 4. P.                                    | 9 mos.            | 2 daily, thick, mushy, much mucus  | normal              | descending colon, sigmoid colon    | All clinical symptoms cleared up after 5 months.                                                                                                                                                                          |
| 5. K. L.                                 | 3½ yrs.           | 5 daily, watery, mucus, blood      | bloody, swollen     | transverse colon                   | Clinical symptoms all disappeared after 6 weeks. Eleven months later X-ray examination negative.                                                                                                                          |
| 6. G.                                    | 3 years           | 4 daily, thin, mushy, blood, mucus | bloody, swollen     |                                    | No subjective complaints after 10 weeks. Stools mushy. No pathological substances present. Three months later arthritis with recurrence of intestinal condition. Revaccination gives improvement. Final result not known. |
| 7. M.                                    | 4 years           | thick, mushy, mucus, blood         | inflamed, ulcerated | descending colon, polyposis        | Temporary improvement. Two and one-half years later, again blood in the stools. Revaccination results in improvement. End result not known.                                                                               |
| 8. Z. W.                                 | 1 year            | thick, mushy, blood, mucus         | hyperemic polyp     | descending colon, polyposis        | Some improvement in general condition.                                                                                                                                                                                    |
| 9. L.                                    | 1 year            | 10 daily, blood, mucus             | bloody, edema       | transverse colon, descending colon | In 10 weeks clinical symptoms disappeared. Seven months later X-ray examination reveals slight departures from the normal. Rectoscopy negative.                                                                           |
| 10. S.                                   | 4 years           | hard, blood, mucus, pus            | bloody              | descending colon, sigmoid colon    | All symptoms disappeared after 14 weeks.                                                                                                                                                                                  |
| 11. H.                                   | 3 mos.            | 1 daily, blood, mucus              | normal              | descending colon                   | No results for 8 weeks. Fresh vaccine given subcutaneously results in improvement.                                                                                                                                        |
| 12. W.                                   | 6 mos.            | 2 daily, mucus, blood              | normal              | transverse colon                   | Clinical symptoms disappeared in 3 months. Six months later again mucus in stools. Revaccination results in recovery and X-ray examination is negative.                                                                   |
| 13. S.                                   | 8 years           | diarrhea, mushy to formed, mucus   | injected            |                                    | Gradual recovery.                                                                                                                                                                                                         |
| 14. H.                                   | 1 year            | diarrhea, thin, mushy              | normal              |                                    | Complete recovery.                                                                                                                                                                                                        |
| 15. M.                                   | 4 mos.            | obstipation, mucus, blood          | red, ulcerated      |                                    | Complete recovery.                                                                                                                                                                                                        |
| 16. v. B.                                | 6 mos.            | diarrhea, blood, mucus, pus        | inflamed            | transverse colon, descending colon | Gradual recovery.                                                                                                                                                                                                         |

One case of patient with diarrhea, bloody mucus in stools and many symptoms of allergy (no diagnosis made)

The stools of 15 patients with various types of diarrhea such as:

Paradoxical diarrhea

Diarrhea in tuberculous enteritis

Gastrogenic diarrhea and diarrhea in typhoid fever were examined and one case found positive

If the intestinal lesions are situated low enough for rectoscopic investigations, it is much better to gather the material directly from lesions found on the intestinal wall, using as far as possible aseptic technique. However, inasmuch as the lesions in a number of cases are beyond the reach of the rectoscope, one of necessity, must attempt the isolation of the germ from the material found in the feces.

**Agglutination:** As we have mentioned, agglutination reactions of the isolated cocci were also used for

identification, as well as study of the morphological and cultural characteristics. To that end we carried on agglutinations with rabbit serum from animals which had received a weekly intravenous injection 3 to 4 times with a concentrated emulsion of dead cocci obtained from our autopsy. However, we assured ourselves that this serum did not agglutinate the cocci before our injections were begun.

To agglutinate the different strains of diplococci with specific rabbit serum, tubes were placed at 37° C. for 4 hours and then at room temperature until the following day at which time the end results were noted. (Table 3).

As appears from the preceding table most strains taken from patients with *colitis ulcerosa* showed a strong agglutination while others were negative in this respect. It may be possible that here as also happens with many other organisms, we are dealing with several varieties of the germ. We also followed up the agglutination reactions with a number of strains

TABLE II

*Bargen's diplococcus was suspended in stomach contents containing free HCL. From the table one can observe that in the presence of acid, the bacteria did not live*

| Name | Free HCL | Total Acidity | Living Bacteria |
|------|----------|---------------|-----------------|
| T    | 34       | 58            | —               |
| K    | 34       | 70            | —               |
| E    | 4        | 34            | —               |
| M    | 44       | 70            | —               |
| V    | 9        | 43            | —               |
| M    | 20       | 46            | —               |
| M    | 9        | 42            | —               |
| B    | 31       | 42            | —               |
| H    | 18       | 52            | —               |
| M    | 7        | 42            | —               |

| Strains             |          | Titer of the Agglutinating Serum (Autopsy Strain) |
|---------------------|----------|---------------------------------------------------|
| K. Z.               | 1 100 +  | 1 100 ++                                          |
| J. P.               | —        | 1 100 ++                                          |
| M. V.               | 1 100 ++ | 1 100 ++                                          |
| B. P.               | 1 100 ++ | 1 100 ++                                          |
| J. G.               | 1 100 ++ | 1 100 ++                                          |
| H. v. L. W.         | 1 100 ++ | 1 100 ++                                          |
| K. Z.               | 1 150 ++ | 1 100 ++                                          |
| Patient Dr. H.      | 1 150 ++ | 1 100 ++                                          |
| Patient Dr. S.      | 1 200 ++ | 1 100 ++                                          |
| Patient Dr. M.      | 1 100 ++ | 1 100 ++                                          |
| J. B.               | 1 25 +   | 1 100 +                                           |
| S. v. d. L.         | —        | 1 100 +                                           |
| J. H.               | 1/15 ±   | 1 100 ±                                           |
| S. d. L.            | —        | 1/100                                             |
| N. N.               | 1 25 +   | 1/100                                             |
| (Patient Dr. v. B.) | —        | 1/100                                             |

isolated from the bowel and stools of individuals in whom there was no evidence of colitis ulcerosa, but which, however, gave the morphological and cultural characteristics of Bargen's diplococcus. Not one of these gave positive agglutination reactions. These tests were done by mixing the bacterial emulsions in different dilutions of the serum, placing for 4 hours at a temperature of 37° C. and leaving at room temperature until the following day at which time the results were read.

**Vaccination:** Patients were generally given a subcutaneous injection every 3 to 4 days of 0.1; 0.2; 0.4; 0.8 and 1 cc. of the vaccine. In this manner the treatment was carried on for not less than 3 months. Vaccination was then discontinued for a few months and again carried out for a couple of weeks. It is recommended that revaccination be repeated at intervals.

In occasional instances, fresh material was isolated from the bowel for the preparation of new vaccine. Circumstances, of course, may make it necessary to make some change in the administration of the vaccine.

#### THE SECRETORY FUNCTION OF THE STOMACH IN ULCERATIVE COLITIS

How the diplococcus causes infection of the bowel is still an open question. Bargen assumed that infected teeth or tonsils might be the focus of infection. Assuming that it is not impossible for the diplococcus to reach the bowel *via* the stomach, it occurred to us to study the influence of the gastric secretions on the

TABLE III

*Results of investigations on stomach contents of patients having colitis ulcerosa. As it is well known that findings differ very much on different occasions, each case was given a test meal 2 or 3 times. Only those examinations showing the highest values are given in the following table*

| Name           | Age | Free HCL | Total Acidity | Pepsin |
|----------------|-----|----------|---------------|--------|
| M              | 29  | 37       | 72            | —      |
| H              | 15  | 35       | 50            | —      |
| P              | 45  | 0        | 38            | —      |
| P              | 15  | 52       | 72            | —      |
| K              | 36  | 0        | 36            | —      |
| G              | 38  | 0        | 16            | —      |
| M              | 27  | 40       | 81            | +      |
| Z              | 64  | 0        | 28            | +      |
| L              | 29  | 0        | 30            | +      |
| S              | 53  | 0        | —             | +      |
| H              | 21  | 20       | 42            | —      |
| W              | 32  | 0        | —             | —      |
| Patient Dr. H. |     | 0        | —             | —      |
| Patient Dr. M. |     | 25       | 42            | —      |

We favored as far as possible, the use of Boas test meal, considering of course, the patients' daily meals. Stomachs were emptied 45 minutes after the test meal. As it is well known that values differ from day to day, the same tests were done on another day. In Table 3, only the highest figures are given. This reveals that in 8 out of 14 cases achylia was present while in 4 patients, pepsin was absent.

Although from the foregoing, no far reaching conclusions can be arrived at, nevertheless, we felt it necessary to report these findings. At any rate, it is remarkable that in a relatively large percent of the patients no acid was present or low acid values were found.

In all patients we examined the stomach contents for the presence of Bargen's diplococcus, which, however, could not be cultured in a single case.

growth of the diplo-streptococcus and to investigate the secretory function of the patient with reference to the presence or absence of hydrochloric acid and pepsin. We suspended the diplococcus of Bargen in stomach contents containing high acid values, low values, and acid free solutions. After about 3 hours in the incubator, these suspensions were inoculated in glucose bouillon. These were then placed in a temperature of 37° C. In those suspensions containing free acid, the diplococci were found dead. (See Table 2). However, if acid was not present they generally survived. (See table 1). The literature shows that opinions differ very much as to the action of HCl in the stomach contents of such patients. Zweig reports achylia in two cases of *colitis ulcerosa*. He considers it not at all unlikely that absence of free acid in the stomach might favorably influence the development of virulent bacteria in the intestinal tract.

Rosenheim noted improvement in a patient who was given HCl with regular gastric lavage.

Körner and Schaefer frequently found no free acid after a Boas test meal. In some cases low acid values were present. Udaondo found achylia in 3 of 11 cases. Schmidt found normal acid values. Albu attaches no importance to the amount of acid in the stomach, for in his opinion, this is subject to very marked fluctuations.

As we have mentioned, our investigations on stomach contents were directed only to the problem of the presence or absence of HCl and pepsin.

# Hepatoptosis\*

By

CHARLES W. McCLURE, M.D., HERMAN A. OSGOOD, M.D.,

and

J. P. BILL, M.D.

BOSTON, MASSACHUSETTS

THIS communication includes the report of a case of hepatoptosis, i.e., total displacement of the liver; the progress of a gumma of the liver observed fluoroscopically and radiographically, and correlation of data obtained from laparotomy or autopsy findings in cases of hepatoptosis reported by other observers. The latter have described the condition under the synonyms "wandering," "movable," "floating" or "prolapsed" liver. Glénard wrote extensively on this subject in 1899 and credits the first case reported to Cantani in 1866. Ssaweljew (2) states that Heister performed the first hepatopepy.

In the report which follows the displacement of the liver could be positively diagnosed by means of contrast medium, which also permitted observations of changes in the gumma present.

## CASE REPORT

A white housewife, aged 50, complained of pain in the right flank of eight years' duration. The mother, aged 70, was alive and well, as also were two sisters and a brother. The father had died of an unknown cause. There was no family history of cancer, metabolic, cardio-vascular, nervous or mental disease. The history of birth showed delivery to have been normal. The patient had had during childhood, measles, mumps, chickenpox, whooping cough, influenza. The catamenia had begun at twelve and continues to date, of the regular twenty-eight day type. It is symptomless other than for a flow for four or five days. The patient had been married eighteen years but there were no children. There had been no pregnancies, although contraceptive measures were not employed. There is no history of headaches or vertigo. A moderate presbyopia is corrected by glasses. There has been no diplopia, or other visual disturbance. In May and June, 1924, the left eyeball was "very painful." No definite diagnosis of the condition was made by the attending physician. There is no other history suggesting iritis or other ocular disease. The hearing is good. There have been no diseases of the ear, nose or throat. The teeth have all been extracted. There is no history of sore mouth or tongue or of skin lesions or loss of hair. There have been no communicable diseases, such as typhoid fever or pneumonia. About eighteen years ago cholecystectomy was performed, at which time the appendix also was removed. No data concerning the findings are available. This operation relieved attacks of marked epigastric distress of three years' duration. The patient's appetite usually had been good. The bowels had been constipated since childhood. There had been no nausea, no vomiting, no hematemesis, no bloody or tarry stools or jaundice.

In 1923 the patient was coasting on a large sled and was lying prone. Sliding down a steep hill the sled went over

a ledge three feet high. When the sled landed, the concussion to the patient's abdomen caused epigastric pain which radiated through to the back to the right of the tenth to twelfth dorsal vertebrae. The pain persisted about ten minutes, and was so severe the patient stated she "felt as if she were split open." In 1925 the patient had an attack resembling grippe lasting about ten days. During this illness, paroxysmal pain developed under the costal margin in the left hypochondrium. It varied in severity from mild to sharp. It was aggravated by deep inspiration. It bore no relation to food and did not disturb sleep. The pain described was occasionally accompanied by mild pain in the ridge of the left trapezius muscle, in the occipital region and in the right flank at edge of ribs below the right axillary region. There were no symptoms referable to the gastrointestinal, cardiorespiratory, genitourinary or neuromuscular systems. The weight was as usual, 133 pounds.

On physical examination a mass was palpable in the epigastrium. It moved with respiration, was smooth, firm in consistency and moderately tender. Its upper border was beneath the ribs. The lower border extended across the region between the ribs of the epigastric notch. The tumor was interpreted as part of the left lobe of the liver. Otherwise physical examination essentially was negative. Fluoroscopic examination of the chest yielded no evidences of intrathoracic lesions. The diaphragm was normal in position and action. The weight was 126.

Hemoglobin was 90 per cent, red cells 5,000,000 and white cells 6,000 per c. mm. of blood. The stained smear showed nothing unusual. The urine showed no albumin, sugar or pathologic elements on microscopic examination.

In May, 1933, the patient again was examined. During the interim since 1925 there had been no communicable, cardiorespiratory, genitourinary or neuromuscular disease. During the last year the weight had fallen from 134 to 113½ pounds. Since 1925, each year the abdominal pain had been present over a period of two to three months; usually during the late winter. The pain developed without relation to exertion or position, but lying on the right side aggravated it. Often it was "excruciating," persisting a few hours to a few days and was localized in the right flank. The pain was accompanied by abdominal bloating and discomfort. The appetite was poor, the bowels were moderately constipated. There was no nausea, vomiting, water brash, regurgitation, borborygmus, peristaltic unrest or other gastrointestinal symptoms other than the pain and discomfort described above.

Physical examination showed a rather poorly nourished woman not appearing seriously ill. The weight was 51.8 kilograms or 114 pounds. Height was 165.5 cm., surface area 1.5 square meters. The trunk measured 88.9 cm. and the chest circumference 73 cm. The total air capacity of the lungs was 3570 cc. Examinations of the following anatomical regions were essentially negative: pharynx, neck, thorax, breasts, lungs, genitalia, extremities, spine, lymphatic glands, nails, cardiovascular and neuromusc-

\*From the Fifth Medical Service of the Boston City Hospital, Boston. Submitted February 10, 1935.

ular systems, and cranial nerves. The various reflexes were normal. There was no Romberg sign. Station, gait, and coordination were normal.

On inspection, the abdomen was full and rounded, whether erect or prone, and the muscles were of normal tone. In the right flank was an oval protuberance 12 cm. long and 5 cm. wide. On palpation the entire right half of the abdomen was filled with a firm, smooth, non-tender, immobile tumor. It extended from the midline of the abdomen to the flank where part of its upper portion formed the protuberance described. The tumor reached to the crest of the right ileum below and above it disappeared under the right costal margin.

Blood pressure was 100 systolic and 45 diastolic. The heart was not enlarged and showed no auscultatory or other abnormalities. The peripheral arteries were not demonstrably sclerosed. The electrocardiogram disclosed the T. wave to be diphasic in the second lead and inverted in the third. There were no other unusual findings.

The audiogram showed normal hearing for both ears.

Examination of the eyes showed no disease. The pupils reacted to light and accommodated normally. Ophthalmoscopic examination showed yellowish optic discs and the retinal vessels appeared fuller than is usual. The color fields plotted normally.

Basal metabolism was + 7%.

Vital capacity was 106% by Dreyer and 111% by West formulae respectively.

Two 24-hour urine collections gave amounts of 1050 and 960 cc. respectively. They were very slightly turbid, acid in reaction and the specific gravity was 1.010. Both specimens showed a slight trace of albumin and no sugar. The sediment after centrifugalization showed no abnormal microscopic elements. Both ureters were catheterized—the urines from both kidneys showed nothing abnormal microscopically. Nitrogen partition was as follows:

|                 | Total N 4.43 gms. | 5.46 gms.       |  |
|-----------------|-------------------|-----------------|--|
|                 | Amount 1050 cc.   | 960 cc.         |  |
| Urea N          | 3.45 gms. 77.6%   | 4.43 gms. 81.1% |  |
| Uric N          | .10 gms. 2.5%     | .09 gms. 1.7%   |  |
| NH <sub>4</sub> | .27 gms. 6.1%     | .28 gms. 5.1%   |  |
| Creat. N        | .22 gms. 5.0%     | .18 gms. 3.3%   |  |
| Resid. N        | .39 gms. 8.8%     | .48 gms. 8.8%   |  |

Phenolsulphonaphthalein excretion in the urine was 59% 59% in 2 hours. These findings are within nonpathological limits.

Hemoglobin was 67% Sahli. Red cells were 4,600,000 and white cells 5,900 per c. mm. of blood. The stained smear showed no abnormal elements. The differential count gave polynuclears 68%, lymphocytes 31% and eosinophiles 1%. Three blood specimens showed positive Wassermann, Kahn and Hinton reactions. Per 100 cc. blood non-protein nitrogen was 28 mgm., urea nitrogen 14 mgm., uric acid 2.5 mgms., creatinin 1.5 mgm. and sugar 104 mgm.

Galactose tolerance was lowered; mellituria occurred after oral administration of both 20 gm. and 10 gm. of galactose. This probably reflected liver functional disturbance.

Duodenal bile was obtained and analysed according to the methods developed by McClure (3). After oleic acid stimulation 50 cc. of pale yellow duodenal bile were obtained. Analyses were made as follows: furfural no., 40; cholesterol, 21 mgm.; alcohol insoluble pigment, 1.5 mgm.; alcohol soluble pigment, 3.0 mgm. These findings show a considerably lowered concentration of bile. This observation and that of lowered sugar tolerance are interpreted as resulting from disturbances of the liver function.

Sigmoidoscopy showed a greatly lessened blood vessel pattern in the rectum with a somewhat grayish mucous membrane. In the sigmoid the blood vessel pattern was absent, the mucous membrane was finely granular and of grayish color. Other than these chronic catarrhal

changes of the mucous membrane, the region was normal.

X-ray findings were as follows:

Films of the skull and sinuses were negative. The sella measured 7 by 11 mm. and was regular in outline.

The chest films showed no evidence of substernal thyroid. The heart and aorta were not enlarged. Except for a single discrete calcified area in the left infraclavicular region the lung fields appeared normal.

Intravenous pyleogram showed good function of both kidneys and a normal filling of both pelves and calyces. A slight rotation of the right kidney on its vertical axis was suggested. Retrograde pyleogram showed a very slight blunting of the minor calyces and infundibulum. This was due to overfilling. The size, shape and anatomical position of the kidneys were normal.

Gastrointestinal barium studies showed no evidences of organic lesions in the stomach, duodenum or bowel. However, these organs occupied only the left half of the abdominal cavity.

After barium enema it was found that the hepatic flexure and ascending colon were displaced downward and mesially by a large tumor mass in the right abdomen. This mass extended downward to the level of the upper border of the fifth lumbar vertebra and overlying it the normal shadow of the right kidney could be seen, the lower pole of which was level with the lower border of the third lumbar vertebra. The size and shape and position of the kidneys were within normal limits. The right diaphragm was not elevated and its costophrenic angle was clear.

Pneumoperitonium was done by introducing 1000 cc. of air through a trocar. Fluoroscopic examination showed a relatively large gas bubble beneath the dome of the right diaphragm. Films showed no shadows in the regions of the epigastrium and left hypochondrium. However, a shadow interpreted as that of the liver occupied the right half of the abdominal cavity from the edge of the ribs to below the crest of the ilium. Between the upper border of this shadow and the air bubble beneath the right diaphragm lay another shadow of undetermined origin. The diagnoses considered were a cyst, a new growth or coils of small intestine.

Because of the uncertainty of the X-ray diagnosis and because the consulting urologist and consulting surgeon urged removal of the palpable tumor it was considered permissible to administer thorium dioxide. Accordingly the commercial preparation "Thorotrast" was given intravenously and satisfactory contrast films were obtained in the prone position. The liver shadow was rotated downward so that the middle and left lobes lay under the dome of the diaphragm and above the right lobe. The right lobe occupied the right half of the abdominal cavity to beneath the crest of the right iliac bone. Various measurements are given in Table I.

TABLE I.

The measurements of the abdominal cavity, liver and spleen shadows.

|                                                              | Date       |            |
|--------------------------------------------------------------|------------|------------|
|                                                              | June, 1934 | Nov., 1934 |
| Transverse diameter of abdomen at attachments of diaphragms: | 34 cm.     | 31.5 cm.   |
| Dome of right diaphragm to iliac crest at expiration:        | 24.5       | 22.0       |
| Excursion of right diaphragm by fluoroscope:                 | 5.0        | 5.5        |
| Left diaphragm by fluoroscope:                               | 4.5        | 4.5        |
| Right lobe of liver, posterior view, vertical:               | 24.3       | 22.0       |
| Transverse at greatest diameter:                             | 16.5       | 13.1       |
| Accessory lobes under right diaphragm, vertical:             | 5.0        | 6.5        |



Fig. 1.

|                                                    |      |      |
|----------------------------------------------------|------|------|
| Accessory lobes under right diaphragm, transverse: | 12.0 | 12.0 |
| Spleen, transverse:                                | 8.5  | 11.3 |
| Spleen, verticle:                                  | 10.5 | 11.3 |
| Left lobe of liver, vertical:                      | 10.5 | 10.5 |
| Left lobe of liver, transverse:                    | 8.5  | 8.0  |
| Lesion in right lobe, vertical:                    | 7.5  | 3.7  |
| Lesion in right lobe, transverse:                  | 9.4  | 3.1  |

In addition to the measurements given in Table 1, within the enlarged right lobe of the liver was a filling defect measuring 7.5 cm. by 9.4 cm. The margins of the area were sharply defined. These findings are readily discernible in the reproduction of the X-ray film (see Figure 1).

The spleen was well outlined on the film. The left border was prolapsed from the diaphragm so that it occupied a position in the mid portion of the upper left abdominal quadrant. The upper pole reached the dome of the diaphragm. It was apparently rotated so that the left border lay anteriorly, as is shown in Figure 1.

*The diagnoses made were:* Displacement of the liver, i.e., total hepatoptosis; tertiary syphilis and gumma of the liver. The trauma was considered the cause of the hepatoptosis and the gumma an incidental finding. The contrast films of the liver, excluding the area of the tumor, showed no defects in the liver substance. This finding goes far to eliminate cirrhosis.

The patient was not given antiluetic treatment until the fall of 1934. This was for the purpose of ascertaining the effects of measures designed to influence the disturbed state of the liver function (4); i.e., the weekly intraduodenal administration of 25 cc. of 33% magnesium sulphate solution. Coincidentally the food intake was augmented. These therapeutic measures were followed by a gain of 33 pounds in weight, disappearance of all subjective symptoms and non-recurrence in 1934 of attacks of pain which had regularly occurred each spring for the past eight years.

Intramuscular administration of bismuth salicylate was instituted in September, 1934. One gram of potassium iodide, the tolerance dose, was ingested daily. Fifteen

Fig. 1. This illustration shows the liver occupying the right abdominal cavity; the left-lobe is beneath the right leaf of the diaphragm and the lower border of the right lobe extends below the crest of the Ilium. The negative shadow within the right lobe represents a gumma. The spleen is outlined beneath the left leaf of the diaphragm.

weeks later a second contrast film was taken. During this period 1.95 grams of bismuth salicylate and 105 grams of potassium iodide had been administered. The changes occurring in the liver are portrayed in the reproduction of the X-ray film (Fig. 2) and in Table I, under November. The changes consist in a definite decrease in the size of the liver and an almost complete disappearance of the gummatous area. The development of these changes had been observed through the fluoroscope by which means progressive increase in density of the liver's shadow was also noted. The position and rotation of the liver remain essentially unchanged.

### DISCUSSION

Various authors describe symptomatology due to displacements of the liver. However, their descriptions are based partly on the findings in cases in which the diagnosis was not proved by laparotomy or autopsy or the use of "Thorotrast." It takes but little experience to teach one that the clinical diagnosis of this condition is fraught with great chances for error. For this reason it is unsafe to correlate the symptoms presented except in those cases in which the diagnosis has been proved objectively. Therefore, the writers have considered it necessary to correlate the symptomatology presented by reported proved cases.

Seventy cases (5 to 51 and 53 to 57 inclusive) of total hepatoptosis, in which the diagnosis was confirmed on laparotomy or autopsy, have been collected. Of the 70 cases only six were men; thus the condition is largely confined to women. The condition was most common between the ages of twenty to fifty, by far the greatest number occurring between the ages of thirty to forty; the youngest was twenty (18) and the oldest sixty-seven (15). Pregnancy had preceded the symptoms in thirty-three of the sixty-four women. In nine the symptoms had developed suddenly and immediately following trauma or unusual physical exertion. Trauma was the apparent cause in our case. Paralysis of the right leaf of the diaphragm due to diphtheria was considered to be the cause in one case (10). The condition was congenital in one case, a mesohepar being found (38). The cause was not discussed in the remaining twenty-six cases. However, with few exceptions these patients were described as splanchnoptotic. This state predisposes to hepatoptosis because pressure of the gastro-intestinal tract is a potent factor in supporting the liver in its normal anatomical position. Obviously, such support is diminished in direct proportion to the degree of laxity of the muscles of the abdomen. Various ligaments are also instrumental in holding the liver *in situ*; principally the lateral, coronary and falciform. Stretching or possibly tearing of these ligaments due to trauma predisposes to displacement of the liver. Such trauma may be incident to violent physical exertion as lifting (26) or carrying a heavy load (16), to jarring as was evidently the cause for the displacement reported here and also by Michl (9) and Langenbuch (10) to blows on the right side (51) or to squeezing of the viscera, as occurred in a case reported by Howell (37) in which a horse rolled over a soldier's abdomen. Thus the usual apparent causes reported for displacement of

Fig. 2. This illustration shows the diminution in the size of the liver and the almost complete disappearance of the gummatous area resulting from antiluitic treatment.



Fig. 2.

the liver are loss of tone of the muscles and trauma to the contents of the abdomen. More rarely the condition is congenital or possibly due to paralysis of the diaphragm.

The case records were often not described in detail; for which reason the frequency, especially of milder symptoms, can not be stated with accuracy. However, the symptoms were sufficiently well described to permit of the establishment of the general symptomatology of the condition.

Of fifty-three uncomplicated cases in which the duration of symptoms was stated it varied from one week to twenty-two years. However, in nearly half the cases it varied from one to two years. The onset was characterized by marked subjective symptoms in twenty-nine while in seventeen the initial symptoms were mild and eventually became more severe. The time of development of the ptosis of the liver is obviously uncertain. Occasionally the patient had observed an abdominal tumor for a considerable period before onset of subjective symptoms, in one case for four years (32). The onset of severe pain and the finding of a palpable tumor which have been observed immediately following strenuous physical exertion or trauma suggest that the ptosis may have an acute onset, as was discussed above.

**Pain.** Fifty-three cases presented hepatoptosis as the sole organic lesion found on laparotomy or autopsy. Of these abdominal pain occurred in forty-seven. The abdominal site of pain was confined to the epigastrium in seven, to the right hypochondrium in twenty-eight, to both these regions in five, to the right hypochondrium and lower abdomen in three, and to the lower abdomen in five. In thirteen of these with upper abdominal pain the latter radiated to the dorso-lumbar back, to the shoulder blades, to the ridge of the trapezius muscle of the right neck, or down the right thigh. The upper abdominal pain was described as of severe paroxysmal character in two, as persistently severe in one and as mild in three. In one case (6) the epigastric pain developed an hour after partaking of food. In six the severe type of pain was at times replaced by mild pain or a sensation of dragging or drawing. This sensation of dragging or drawing was the only abdominal discomfort experienced by two other cases. In three of these there were no symptoms but attacks of vomiting occurred in the three other cases. In one case the lower abdominal pain was described as of severe colicky nature. In eight cases exertion aggravated the pain while reclining relieved it. In three of these eight cases bending produced a sensation of intra-abdominal pressure.

The experimental observations of Steele (52) on cadavers indicate that the abdominal pain may result from kinking or torsion of the cystic or common ducts due to the dropping of the anterior portion of the liver. However, in the case reported here the pain occurred only at one season of the year and this obscures the explanation of its mechanism. Jaundice developed in seven cases in which severe pain occurred in either the upper or lower abdomen, and in another case in which the pain was mild. Jaundice developed in one other case characterized by chills and

fever (19) and in which abdominal pain did not occur. In another case (15) the chills and fever were accompanied by abdominal pain but jaundice did not develop.

**Associated symptoms and signs.** In two cases (6, 48) attacks of hematemesis and melena occurred; in these, upper abdominal pain was a prominent symptom. One case (32) presented dyspnoea and mild cough, in addition to attacks of severe epigastric and dorsolumbar pain. Attacks of gross hematuria occurred in one case (15), great frequency of urination in another (26) and scalding urination in a third (20). In another case (46) oliguria was followed by polyuria in a manner comparable with that which may occur in intermittent hydronephrosis. On laparotomy no kidney lesions were found in these four cases and the urinary symptoms were relieved by hepatoexy. In two cases (32, 42) light edema of the lower extremities was present. In another case (31) paroxysmal attacks of tachycardia occurred which were relieved after hepatoexy. Vomiting was a prominent symptom in sixteen cases, in only one of which (19) was abdominal pain absent. In one of these (31) vomiting was frequent and on various occasions "gastric peristaltic waves were plainly visible" on inspection of the abdomen. At laparotomy the stomach and intestines of this case (31) appeared to be normal. The vomiting and visible peristalsis were interpreted as the result of occlusion of the pylorus due to pressure of the displaced liver on the stomach. Anorexia, diarrhea, bloating and other dyspeptic symptoms were present in twenty-one cases. The general or nervous symptoms, headache, lassitude, malaise, nervous irritability, dizziness, fatigue, cold and hot flashes, insomnia, melancholia, were present to well marked degrees in thirteen cases. In three cases (5, 19, 22) there were no subjective symptoms.



Thus the *symptoms presented by fifty-three uncomplicated cases* may be classified as:

1. Hepatic; *i.e.*, pain, jaundice, chills, fever.
2. Gastro-intestinal; *i.e.*, nausea, vomiting, anorexia, diarrhea, constipation, obstipation, hematemesis, melena.
3. Cardio-respiratory; *i.e.*, dyspnoea, cough, edema, tachycardia.
4. Genito-urinary; *i.e.*, hematuria; great frequency urination; dysuria.
5. General; *i.e.*, headache, malaise, lassitude, weakness, nervous irritability, dizziness, fatigue, cold and hot flashes, insomnia, melancholia.
6. Latent; *i.e.*, no subjective symptoms.
7. Accessory or secondary: sensation of tumor in abdomen on bending (6); pain aggravated by exertion and relieved by reclining.

Both abdominal pain and jaundice occurred in sufficient numbers of uncomplicated cases to establish them as symptoms and signs resulting from the displaced liver. Chills and fever without jaundice but with pain was recorded in but one patient. However, repeated attacks of these symptoms were relieved entirely by hepatoxy, at which operation no other pathology were discovered. The gastro-intestinal symptoms may all be logically explained as due to pressure of the displaced liver and interference with the portal circulation. The genito-urinary symptoms enumerated were well marked in the four patients in which they were observed. While pyleograms were not done; at operation no pathology other than the displaced liver was found and hepatoxy entirely relieved the symptoms. These findings indicate that the displaced liver, possibly through pressure phenomena, produced these urinary symptoms. There is no reasonable doubt but that the accessory or secondary symptoms described were the result of the liver's abnormal position. Obviously, the explanation of the general symptoms is problematical. They also were relieved by hepatoxy and this finding indicated that the symptomatology described was incident to displacement of the liver. Dyspnoea and cough on exertion occurred in one case (32) and paroxysmal attacks of tachycardia (31) in another. In both cases hepatoxy was followed by disappearance of the symptoms. However, neither the pulmonary or cardiovascular systems were subjected to radiographic, electrocardiographic and other searching studies which are necessary to rule out disease. For this reason the findings merely suggest that the pulmonary and cardiac symptoms described resulted from displacement of the liver. Nevertheless these symptoms of dyspnoea, cough and tachycardia may logically be explained as due to disturbances in cardiac action resulting from traction of the vena cava on the heart as a result of the pull of the displaced and mobile liver. In two other cases mild, but definite, edema of the lower extremities occurred. Hepatoxy relieved the edema in one case (45). The other case (39) came to autopsy and no cardio-vascular pathology was found. In both these cases the edema is explained as resulting from pressure or a kinking of the inferior vena cava.

In fifty-three uncomplicated cases the liver was not demonstrably diseased. In a fifty-fourth case (38) an old gumma was found which in no way influenced the subjective or objective symptomatology. This finding is comparable with that in the case reported in this communication. In another, the fifty-fifth case, au-

topsy disclosed uniformly distributed atrophy of the liver cells incident to the obstructive jaundice. The latter was due to kinking or torsion at the commencement of the common bile duct. In three cases the liver, *i.e.*, an abdominal tumor, was not palpable. In the fifty uncomplicated cases in which the liver was palpated, it occupied the right upper abdominal quadrant in twenty-three; it reached into the midabdominal quadrant in ten and occupied the entire right side of the abdomen in twelve. It was palpable in only the right lower abdominal quadrant in five cases. The liver was described as freely movable on palpation in twenty-six cases, as smooth in six, hard in six and soft in two, an edge was felt in one and a notch in another; it was tender on palpation in two and moved on respiration in three cases. Unusual descriptions of palpatory findings were that the tumor was "fist-sized" in three cases and the "size of a child's head" in another. The usual area of liver dullness over the lower anterior chest was replaced by a tympanitic note in five cases. In two of these, pushing the abdominal tumor up under the right ribs brought about a change in percussion note from tympany to dullness (40, 39).

In twenty-seven of the uncomplicated cases the *mobility* of the palpable abdominal tumor; *i.e.*, the liver, was not described. However, on laparotomy or at autopsy the liver was readily replaced in its normal or nearly normal anatomical site. From this finding it is inferred that the liver palpated preoperatively as an abdominal tumor was freely movable in these cases. Thus, mobility of a palpable abdominal tumor in the right side of the abdomen is the usual finding in hepatoptosis. Tenderness on palpation was noted in but two cases which permits the deduction that the ptosed liver is usually not sensitive to ordinary palpation. The liver of the case reported here was not tender on palpation.

*Thus, the usual findings in hepatoptosis may be summarized as a freely movable, non-tender tumor occupying the right abdomen.* The upper border is usually under the right rib margins and the lower border anywhere from the mid portion of the right hypochondrium to below the crest of the right ilium; the entire tumor may be situated below the costal margins, even in the right lower quadrant. While the tumor mass usually appears large, it may occasionally on palpation be apparently as small as a "fist." Rarely, no tumor is palpable. When occasionally there is absence of normal liver dullness over the lower right chest such dullness may be returned by pushing the tumor up under the margins of the ribs on the right.

Eleven *incorrect preoperative diagnoses* were made, which are as follows: hydronephrosis (34); floating kidney (9, 10, 11, 20, 22, 25); tumor of gall bladder (36); gall stones (36); enlarged liver (9, 36); echinococcus cyst (7, 25, 32); liver abscess (19); cancer of the liver (32); tuberculous typhlitis (14); renal tumor (49); and subdiaphragmatic abscess (44).

The following *complications* were demonstrated in sixteen of the seventy cases: chronic cholecystitis (6); pericholecystitis (6); cholelithiasis (9, 44, 46, 49); duodenal ulcer (6); cirrhosis (13, 21, 7, 22); single cicatrized gumma (38); hydatid cyst (44); cancer (51); duodenal ulcer with pyloric stenosis (53); floating kidney (20, 50, 55); hydronephrosis (8). In another case, as already described, atrophy of the liver parenchyma was found.

All but a relatively few of the cases which have been correlated were subjected to some form of hepatopepy; the results of which were highly favorable. Comparable conclusions are reported by Treves (57), Ssaweljew (2), Werner (8) and others who have collected the postoperative results of published hepatopepies.

### SUMMARY

A case of hepatoptosis is reported in which the positions and anatomical characters of the various intra-abdominal organs were definitely established by X-ray films of the untreated abdomen, by pyelography, by barium gastrointestinal studies and by pneumoperitoneum. The exact positions of the spleen and liver were established by contrast X-ray films after intra-

venous administration of "Thorotrast," a colloidal suspension of thorium dioxide. By means of this contrast medium, other than for a gumma, anatomical lesions such as cirrhosis were probably excluded. This medium permitted radiographic demonstration of diminution in size of the liver and the contained gummatous area resulting from antiluetic treatment.

Fifty-three uncomplicated cases of hepatoptosis, or total displacement of the liver, have been collected from the literature and the described symptomatology correlated.

The reported results of hepatopepy indicate that the operation is an efficient measure for relieving symptomatology.

### REFERENCES

- Glénard, Frantz.: Les Ptoses Viscérales, Diagnostic et Nosographie. Félix Alcan, Paris, 1899.
- Ssaweljew, N.: Hepatoptose, Verlagerung der Leber. *Arch. f. klin. Chirurg.*, Berl., 70:644, 1903.
- McClure, Charles W.: Functional Activities of the pancreas and liver. A study of objective methods for the estimation of function levels in health and disease. To be published.
- Mendenhall, Walter L.; Charles W. McClure and Mildred Cate.: Chologogic properties of magnesium sulphate. *Bost. Med. and Surg. Jour.*, 195:176, 1926.
- McClure, C. W.; W. L. Mendenhall, and Mildred E. Huntsinger: The evaluation and treatment of disturbed liver function. *J. A. M. A.*, 85:1537, 1925.
- Pendergras, Eugene P., and Elizabeth Kirk: Significance of gas under the right dome of the diaphragm. *Am. Jour. Roentgenol.*, 22:238, 1922.
- Kaiser, J.: Die Wanderleber und ihre erfolgreiche Behandlung. *Deutsch. Ztschr. f. Chirurg.*, 175:411, 1922.
- Gross, W.: Verfahren zur Leberbefestigung bei Lebersenkung und eine Beziehung für die Grösse einer Magensenkung. *Deutsch. med. Wschr.*, 41:1460, 1915.
- Werner, Karl: Ueber einen Fall von hochgradiger Hepatoptose verbunden mit verschleiblicher intermittierender Hydronephrose. Inaug.—Dissert., München, 1907.
- Miehl: De la fixation du foie mobile. *Congrès Internat. de Méd.*, Moscou, 5:126, 1897.
- Langenbuch, C.: Die Wanderleber. *Deutsche Chirurgie. Chirurgie der Leber und Gallenblase (zusätzlich der Gallenwege)*. II Teil. Fennlin und Enke, Stuttgart, 1897, pp. 138.
- Langenbuch, C.: Freie Vereinigung der Chirurgen Berlins. III. Vorstellung eines Falles von operativ geheilter Wanderleber. *Berl. klin. Wschr.*, 28:69, 1891. Ibid.: Kleinere Mitteilungen. 14) Freie Vereinigung der Chirurgen Berlins. *Berl. klin. Wschr.*, 28:82, 1891.
- Desguin, Leon: Statistique generale des opérations pratiquées pendant l'année 1891. *Ann. and bull. de la soc. de méd. d'Anvers*, 54:205, 1892.
- Lincolne et Faquet: Hépatoptose totale; foie cirrhotique; hénatopexie. *Gaz. hebdom. d. sc. méd. de Bordeaux*, 16:41, 1895.
- Richelot, L. G.: Fixation d'un foie déplacé. *Gaz. hebdom. de méd. de chirurg.*, 30, série 2:342, 1893; and *Union méd.*, Paris, 56:169, 1893.
- Depnec, A., and L. Mayer: Die chirurgische Behandlung der Hepatoptose durch Laparektomie und Hepatopexie. *Arch. f. klin. Chirurg.*, 73:1081, 1904.
- Ibid.: Ueber Hepatoptose, 312:112, 1904.
- Michl: Note sur un tiraillement douloureux à distance dans le foie mobile. *Gaz. des hop.*, 70:335, 1897.
- Treves, Frederick: The treatment of Glénard's disease by abdominal section. *Brit. Med. Jour.*, 1:1, 1896.
- Aréiza: Quoted by Böttcher, reference no. 32.
- Blanc: Hépatopexie pour une hépatoptose totale. *Lyon méd.*, 86:227, 1897.
- Pean: La luxation du foie et du rein.—Son traitement par un procédé spécial. *Cong. Franc. de chirurg.*, 10:490, 1896.
- Delangenière, Henry: Cirrhose hépatique et hépatoptose.—Hepatopexie et cholécystostomie; guérison. *Bull. et mem. soc. de chir.*, Paris, n.s., 23:232, 1897.
- Franke, Felix: Zur Technik der Hepatopexie. *Centralbl. f. Chirurg.*, 23:775, 1896.
- Bobrow, A. A.: Ein Fall von Hepatoptose (Annen der russ. chirurgie. 1896, Hft. 3). *Centralbl. f. Chirurg.*, 23:990, 1896.
- Ramsay, F. Winsan: Fixation of liver and both kidneys in a case of Glénard's disease. *Brit. Med. Jour.*, 1:1152, 1897.
- Chavillier—Technique de l'Hepatopexie (Procédé de Legue). Thèse de Paris, 1898.
- Depnec: De l'intervention chirurgicale dans la splénoptose et en particulier dans l'hépatoptose. *Nouveaux procédés opératoires. Ann. d. l. soc. belge de Chirurg.*, Bruxelles, 1:297, 1893, 1894.
- Ferrari, P.: Di un caso singolare di epatopexia curata colla epatopexia. *Arch. ed atti d. soc. ital. di chir.*, Roma, 11:61, 1897.
- Gioranno, Davide: Un caso di epatopexia e di fibromioma uterino curato colla epatopexia ed isterectomia. *Gaz. degli osped. e d. cliniche*, 2:1479, 1900.
- Carstens, J. H.: The fixation of a movable liver and report of a case of hepatoptosis. *J. A. M. A.*, 38:1294, 1902.
- Jonas, A. F.: The use of the gall bladder to restore a prolapsed liver. *J. A. M. A.*, 38:803, 1902.
- Ellsworth, Elliot: Hepatoptosis complicated by gastroptosis; a suggestion as to treatment. *Med. News*, 85:913, 1904.
- Rosenow, W. N.: Ueber Hepatoptose. *Allgemeine med. Centralzeit.*, 73:713, 1904.
- G. noville: Foie mobile simulant un rein mobile. Hépatopexie. Guérison. *Arch. d. mal. des organes génito-urin.*, Paris, 16:1281, 1895.
- Howell, John: Rotation of the liver on its vertical axis. *Brit. Med. Jour.*, 1:218, 1917.
- Böttcher, Carl: Ueber Hepatoptose. *Deutsch. Ztschr. f. Chirurg.*, 56:262, 1900.
- Elliot, Ellsworth: Result of operation for hepatoptosis after five years. *Ann. Surg.*, 51:258, 1910.
- Howell, John: Rotation of the liver on its vertical axis. *The Clin. Jour.*, 43:69, 1919.
- Clarke, Thomas W., and David H. Dolley: A case of congenital hepatoptosis, showing a mesopneic. *Am. Jour. Med. Sc.*, n.s., 130:696, 1905.
- Wereluss, Axel: Hepatoptosis and hepatopepy. *J. A. M. A.*, 58:610, 1912.
- Ssaweljew, N.: Hepatoptose, Verlagerung der Leber. (Ätiologie, Symptomatik, Diagnose, Behandlung). Case No. 2. *Arch. f. klin. Chirurg.*, Berl., 70:644, 1903.
- Graham, J. E.: Displacements of the liver. *Trans. Assoc. Am. Phys.*, Phila., 10:258, 1895.
- Crawford, Raymond: A case of anteverted wandering liver. *Lond. Lancet*, 2:1182, 1897.
- Packard, Frederick A.: A case of movable liver. *Trans. Coll. Phys.*, Phila., 3 s., 18:230, 1895.
- Nodwill, Courtney: Ptosis of the liver. *Lond. Lancet*, 2:914, 1901.
- Feder, Irving: Ueber Hepatoptose. *Wien. klin. Wschr.*, 212:1657, 1905.
- Newman, David: Case of movable liver with greatly distended gall bladder, relieved by cholecystostomy. *Glasgow Med. Jour.*, 58:294, 1902, and *Brit. Med. Jour.*, 2:249, 1902.
- Miller, Irving: Hepatoptosis. *Am. Jour. Med. Sc.*, 47:192, 1903.
- Macnaughton-Jones, H.: Recurrent hematemesis due to complete hepatoptosis discovered by laparotomy. *Med. Press and Circ.*, Lond., 65:507, 1898 and *Lond. Lancet*, 1:1327, 1898.
- Truht, J.: A wandering liver: report of a case with clinical remarks. *Obst. Gaz.*, Cinn., 5:337, 1882.
- Peters, George A.: A case of displaced liver, diagnosticated, and operated on, as a case of hydronephrosis, displacement of all the abdominal viscera. *Mid. Gaz.*, 9:113, 1882.
- Binnie, J. F.: Floating liver, with report of a case. *Internat'l Jour. Surg.*, 5:332, 1892.
- Steele, J. Dutton: Experimental evidence of biliary obstruction in floating liver. *Univ. Penn. Med. Bull.*, 15:421, 1902-03.
- Nikolic, Petar K.: Hepatopexie bei Cirrhosis hepatis. *Wien. klin. Wschr.*, 18:1009, 1905.
- Gray, Irving: Medical conditions simulating the acute surgical abdomen. *Med. Times and Long Island Med. Jour.*, 62:269, 1934.
- Ceruzzi, Prof. Aldo: Contributo alla cura operativa delle epatopexie. *Ref. med.*, 262:877, 1910.
- Mosti, Renato: Nouve contributu alla epatopexia. *Ref. med.*, 35:1090, 1919.
- Treves, Frederick: Ptosis of the liver and the "floating lobe." *Lond. Lancet*, 1:1339, 1900.

# Liver Function in Hepatic and Extrahepatic Diseases\*

## II. Clinico-pathological Correlation and Evaluation of the Usefulness of Liver Function Tests

By

G. R. BISKIND, M.D.  
T. L. ALTHAUSEN, M.D.  
G. K. WEVER, M.D.

and

Wm. J. KERR, M.D.  
SAN FRANCISCO, CALIFORNIA

**I**N the course of our liver function studies\*\*, 29 of the patients had abdominal operations with biopsy of the liver, or came to necropsy. This made possible a study of the relationship between the histologic structure and the function of the liver as determined by liver function tests.

### A. INTRINSIC DISEASES OF THE LIVER

The greater proportion of patients in this group (Table I) had a biliary type of portal cirrhosis; the remainder were examples of toxic cirrhosis. Banti's disease, hemochromatosis, syphilis of the liver, and diffuse scarring of the liver following old and recent portal thrombosis.

In all of these patients there was abnormal retention of the dye. The modified glucose tolerance test was markedly positive in the four patients in whom it was performed. The two patients who showed the most marked impairment of excretion of the dye also showed the greatest degree of structural alteration of the liver. These two case histories are presented in more detail:

D. W., No. 42, a white female, 33 years of age, was observed in the University of California Hospital and in the Out-patient Department for a period of ten months, beginning April, 1932. She had contracted syphilis in 1926, and was treated intermittently with bismuth and arsenicals. Several months before entry into the hospital on June 13, 1932, the patient received 25 injections of nearsphenamin in another clinic. She had consumed an excessive amount of alcohol over a period of many years. At entry, examination showed icteric skin and sclerae, a markedly enlarged liver, and a slightly enlarged spleen. The Rose Bengal test was 88 and 86 per cent of the standard at 8 and 16 minutes, respectively. The icterus index was 20. The jaundice subsided after one month and did not recur. She had numerous small esophageal hemorrhages, and 10 months after entry died, following a massive hemorrhage. The last of three Rose Bengal tests was done 2 months before death, showing a retention of 82 and 70 per cent of the dye at 8 and 16 minutes, respectively. The icterus index at the same time was 12 units. At autopsy the liver weighed 2050 grams, was finely

nodular throughout, and yellowish-white in color. The histologic structure, as shown in photomicrograph No. 1, is that of a toxic cirrhosis.

C. P., No. 65, a white male, 50 years of age, entered the University of California Hospital on August 22, 1933, complaining of jaundice, swelling of the abdomen and edema of the ankles, increasing in severity over a period of two months. For the past 30 years he had consumed a quart of wine daily. On examination, he had an icteric skin and sclerae, and evidence of collateral circulation in the flanks and over the abdomen. Even after removal of 4500 cc. of fluid from the abdomen, the liver and spleen were not palpable. There were external and internal hemorrhoids. The Rose Bengal readings were 82 and 79 per cent at 8 and 16 minutes. The icterus index was 60. During the residence in hospital he had several episodes of hematemesis and died following rupture of an esophageal varix. At autopsy the liver weighed 1900 grams, had a yellowish-green color, and was composed of nodules 1 to 2 mm. in size, which completely replaced the normal architecture. Photomicrograph No. 2 represents the histologic structure of the liver. The diagnosis was biliary cirrhosis.

In four patients, clinical examination failed to reveal indications of hepatic insufficiency, although an enlarged liver and spleen were present. The Rose Bengal test showed abnormal retention of dye in all these patients, and the modified glucose tolerance test was strongly positive in one. Subsequent examination of the liver bore out the accuracy of the tests. The salient features of the four case histories are noted:

J. T., No. 91, a 41 year old white female, entered the University of California Out-patient Department on July 1, 1932, stating that she had accidentally noticed a large mass in the left upper quadrant of her abdomen. There were no other complaints. A diagnosis of syphilis had been made in 1909, and she had been treated with several mercury rubs. Examination showed an enlarged, irregular liver, and a greatly enlarged spleen extending almost to the iliac crest. The blood Wassermann reaction was positive. The Rose Bengal test showed retention of 66 and 50 per cent of the dye at 8 and 16 minutes. The patient was treated with potassium iodide, mercury salicylate and bismuth, with no reduction in the size of the liver or spleen. A splenectomy was performed on November 10, 1932, and a biopsy of the liver was taken at the

\*From the Department of Medicine and Department of Pathology of the University of California Medical School, San Francisco.

\*\*See Part I, The Results of Clinical Experience with 326 Cases. Submitted January 8, 1935.

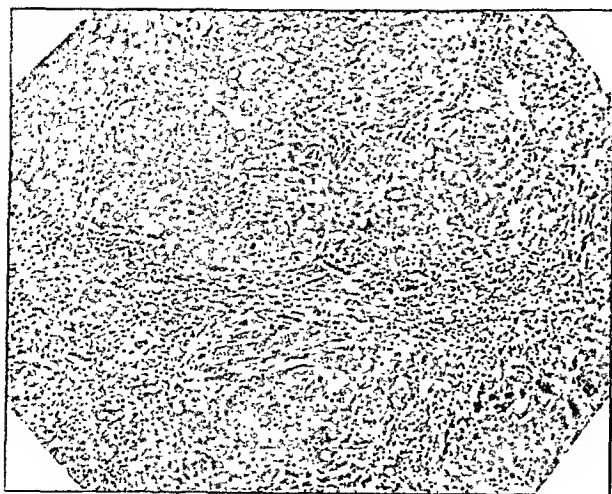


Fig. 1

same time. At the time of operation, the Rose Bengal test readings were 65 and 44 per cent, respectively. The modified glucose tolerance test showed a minimum blood sugar of 52 mg. per cent and a fall of 46 mg. per cent. The icterus index was 8 units. The pathologic diagnosis was syphilis of the spleen and liver. Following the operation, retention of Rose Bengal increased to 78 and 52 per cent, respectively. Since that time the patient has been treated with bismuth and potassium iodide, and examination on June 1, 1934 revealed the liver to be palpably enlarged, but with a smooth edge. The lost Rose Bengal test gave readings of 60 and 40 per cent, respectively. Figure No. 3 shows the microscopic appearance of the liver at the time of operation.

H. K., No. 64, a 51 year old while male, first entered the University of California Hospital on January 7, 1933, complaining of slight dyspnea which occasionally came in paroxysms with orthopnea; and substernal pain. He had been given digitalis since July, 1932. Syphilis was denied. Examination showed the classical signs of aortic insufficiency due to probable aortic valvulitis. The liver and spleen were greatly enlarged. The Rose Bengal test showed retention of 70 and 50 per cent of the dye at 8 and 16 minutes. In September, 1932, a positive blood Wassermann reaction was found on examination in the Out-patient

Fig. 1. (Case No. 42, Table 1). Liver from a patient with toxic cirrhosis. The section shows atypical regenerating hepatic lobules situated in scar tissue. X 100.

Department, and specific treatment started. The patient became irrational and committed suicide on June 24, 1933. At autopsy the gross appearance of the liver suggested chronic passive congestion. However, microscopic examination revealed a picture of early biliary cirrhosis, as indicated in photomicrograph No. 4.

D. B., No. 72, a white male, 17 years of age, had been observed in this hospital since April, 1931. At that time he entered, complaining of intermittent pain in the left upper quadrant of the abdomen for a period of one year, becoming more severe during the previous four months. He was born in Italy and had entered this country when four years old. Examination revealed a greatly enlarged, firm spleen. The liver was not palpable. The white blood count during the first entry varied around 3000 cells per cu. mm. The Rose Bengal test gave readings of 62 and 50 per cent, respectively. The icterus index was 7. He re-entered the hospital after two years with the same complaints. He had gained 31 pounds. The spleen had enlarged slightly; the liver edge was not palpable. His white cell count was 3400 cells per cu. mm. The ability of the patient to excrete Rose Bengal and the icterus index were practically unchanged. A splenectomy and biopsy of the liver were performed on March 7, 1933, and the pathologic diagnoses were "spleen compatible with Banti's disease, and peri-portal cirrhosis of the liver". The latter is illustrated in photomicrograph No. 5.

F. C., No. 252, a 45 year old white Italian male, entered the University of California Hospital in February, 1931, complaining of weakness and pallor of seven months' duration. Examination revealed an icteric skin and a palpably enlarged spleen. Laboratory studies showed an anemia, and indicated that the condition was a chronic hemolytic icterus, probably of the acquired type. A splenectomy was performed on February 6, 1931. Following this the patient remained anemic, notwithstanding liver and iron therapy, but he did not require blood transfusions. He had occasional crises of deglobulinization. The Rose Bengal test gave readings of 59 and 39 per cent in June, 1933, and of 70 and 52 per cent in October, 1933. On

TABLE I  
Intrinsic Diseases of the Liver

| Case No. | Clinical Diagnosis                                       | Icterus Index | Rose Bengal Test |         | Modified Glucose Tolerance Test |       | Pathological Diagnosis                                   | Origin of Material |
|----------|----------------------------------------------------------|---------------|------------------|---------|---------------------------------|-------|----------------------------------------------------------|--------------------|
|          |                                                          |               | 8 min.           | 16 min. | Low                             | Diff. |                                                          |                    |
| 42       | Cirrhosis; syphilis                                      | 12            | 82%              | 70%     |                                 |       | Toxic cirrhosis                                          | Autopsy            |
| 58       | Obstructive biliary cirrhosis; pancreatitis with calculi | 66            | 51%              | 28%     |                                 |       | Biliary cirrhosis                                        | Autopsy            |
|          |                                                          | 25*           | 70%              | 50%     |                                 |       | Pancreatitis with calculi                                |                    |
| 59       | Biliary cirrhosis                                        | 43            | 80%              | 60%     | 40                              | 49    | Biliary cirrhosis                                        | Biopsy; autopsy    |
| 62       | Cirrhosis                                                | 7.1           | 65%              | 50%     | 27                              | 44    | Biliary cirrhosis                                        | Autopsy            |
| 64       | Syphilitic heart disease                                 |               | 70%              | 50%     |                                 |       | Early biliary cirrhosis                                  | Autopsy            |
| 65       | Cirrhosis                                                | 60            | 82%              | 79%     |                                 |       | Biliary cirrhosis                                        | Autopsy            |
| 66       | Cirrhosis                                                | 37            | 74%              | 48%     | 40                              | 51    | Biliary cirrhosis<br>(? Banti's syndrome)                | Autopsy            |
| 72       | Banti's syndrome                                         | 7             | 76%              | 48%     |                                 |       | Periportal fibrosis                                      | Biopsy             |
| 80       | Hemochromatosis                                          | 12            | 71%              | 41%     |                                 |       | Hemochromatosis, with pigment cirrhosis                  | Autopsy            |
| 91       | Visceral syphilis                                        | 8             | 65%              | 44%     | 52                              | 46    | Syphilis of liver and spleen                             | Biopsy             |
| 252      | Chronic hemolytic jaundice                               |               | 70%              | 52%     |                                 |       | Old and recent portal, splenic and mesenteric thrombosis | Autopsy            |

\*2 years later.

Note: In case of repeated tests, the results of the test nearest to the date on which the pathological specimen was obtained, are given.

Fig. 2. (Case No. 65, Table 1). Liver from a patient with biliary cirrhosis. The section shows atypical hepatic lobules associated with marked bile-duct proliferation. X 50.

March 16, 1934, he developed fever with constant epigastric pain and increasing weakness. This persisted for three weeks. During this time the red blood count varied between 980,000 and 2,500,000 cells per cu. mm. Death occurred April 5, 1934. The autopsy showed old and recent thrombosis of the portal, splenic and mesenteric veins. This process extended into the liver, producing numerous small scars. The original thrombosis probably followed the splenectomy in 1931, and caused the focal scarring of the liver. Recanalization then took place, followed by thrombosis as a terminal feature. The effect of the scarring process manifested itself by a decreased excretory function late in 1933, and if another test had been performed in 1934 a still greater retention of the dye probably would have been observed. Photomicrograph No. 6 shows the scarring, together with the recent and old thrombosis of the portal vein.

#### B. OBSTRUCTION OF THE COMMON BILE DUCT

The livers of five patients in this group who had tests of hepatic function, were examined pathologically (Table II). Primary carcinoma of the common bile-duct with complete occlusion was found in patients No. 144 and 152. In patients No. 60 and 156, the obstruction was due to gall-stones in the common duct. The obstruction was complete in the former patient, partial in the latter, in which the liver was also seeded with metastases from a carcinoma of the gall-bladder. In patient No. 6, a biopsy of the liver gave evidence of biliary obstruction, but an exploratory operation failed to reveal its cause. The clinical diagnosis was catarrhal jaundice. The Rose Bengal test showed impaired hepatic function in all five patients of this group, as did the modified glucose tolerance test in the four patients examined.

#### C. NEOPLASMS OF THE LIVER

In patients No. 164 and 147 (Table III), the livers were seeded with metastatic carcinoma, but there was no evidence of common duct-involvement. A slight obstruction of the intrahepatic bile-ducts had caused jaundice, as shown by the icterus index. In patient No. 153, the metastases were very few and there was

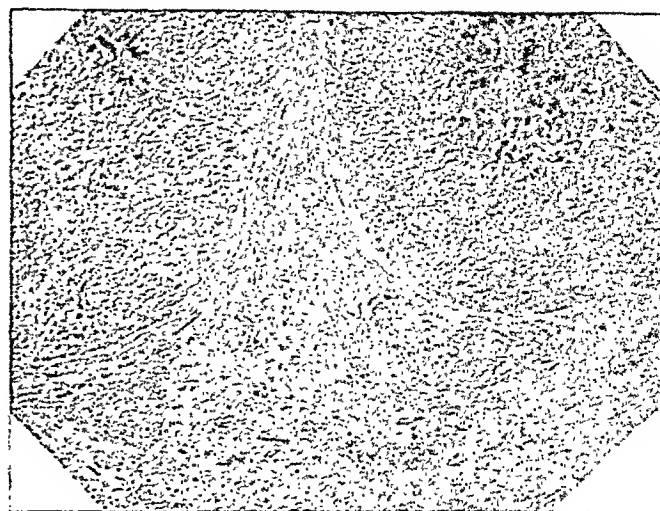


Fig. 2

normal excretion of Rose Bengal and no jaundice. A very diffuse primary endothelioma, simulating metastatic carcinoma in its gross appearance, was found in patient No. 326. The extreme distortion of the hepatic parenchyma, with intrahepatic bile duct obstruction produced by the neoplasm, had caused marked retention of the dye. In patient No. 178 the portal spaces were involved by a leukemic process, but the hepatic parenchyma escaped.

#### D. EXTRAHEPATIC DISEASES

The group of patients listed in Table IV served as controls, since pathological examination of their livers showed no primary hepatic involvement. All but one had a normal liver function, as measured by the Rose Bengal test. Patient No. 240 had a definite retention of the dye, but a biopsy of the liver showed this organ to be normal. The pertinent facts of this case history are summarized below.

E. C., No. 240, a white female, 38 years of age, entered the University of California Hospital in January, 1934, complaining of anemia of 12 years' duration, associated with intermittent pain in the right upper quadrant, tingling of the arms and legs, nausea, and "yellow-skin". The anemia had been variously treated, without improvement. Examination revealed a palpable liver edge and edema of the ankles. The red blood count varied between one and two million red blood cells per cu. mm., and slowly rose to three million. A ligation of the splenic artery was performed on April 7, 1934, and a biopsy of the right lobe of the liver was taken at that time. The liver had a normal gross appearance, but was slightly enlarged when examined during the operation. Its histologic structure was normal. The clinical diagnosis was anemia of undetermined etiology. The Rose Bengal test at that time gave readings of 80 and 51 per cent, respectively. The icterus index was 12 units. Four months later, with an improvement of anemia, the Rose Bengal elimination increased, the readings being 66 and 46 per cent at 8 and 16 minutes.

In patient No. 198, an hepatic lesion was suspected on clinical grounds, but the Rose Bengal test was normal. At autopsy, the liver was found to be normal.



Fig. 3.

Fig. 3. (Case No. 91, Table 1). Liver from a case of syphilis with hepatic involvement. The section shows syphilitic granulation tissue surrounding an hepatic lobule. X 100.



TABLE II  
Obstruction of the Common Bile-Duct

| Case No. | Clinical Diagnosis                  | Icterus Index | Rose Bengal Test |         | Modified Glucose Tolerance Test |       | Pathological Diagnosis                                           | Origin of Material |
|----------|-------------------------------------|---------------|------------------|---------|---------------------------------|-------|------------------------------------------------------------------|--------------------|
|          |                                     |               | 8 min.           | 16 min. | Low                             | Diff. |                                                                  |                    |
| 6        | Catarrhal jaundice                  | 20            | 70%              | 43%     |                                 |       | Liver showing changes due to biliary obstruction; no cause found | Biopsy             |
| 60       | Cholelithiasis; choledocholithiasis | 52            | 63%              | 50%     | 65                              | 72    | Early biliary cirrhosis; cirrhosis; choledocholithiasis          | Biopsy             |
| 144      | Obstruction of common bile-duct     | 110           | 85%              | 76%     | 34                              | 57    | Carcinoma of the common bile-duct                                | Autopsy            |
| 152      | Obstruction of common bile-duct     | 115           | 71%              | 65%     | 59                              | 28    | Carcinoma of the common bile-duct                                | Autopsy            |
| 156      | Metastatic carcinoma of the liver   | 16            | 73%              | 65%     | 59                              | 43    | Carcinoma of the gallbladder; choledocholithiasis                | Autopsy            |

The important findings of this case history are as follows:

C. H., No. 198, a white male, 48 years of age, entered the University of California Hospital in February, 1934, in a state of delirium of two days' duration. It was said that he had consumed large quantities of alcoholic liquors until two years ago; since then he had been on only occasional sprees. Examination revealed a markedly undernourished and dehydrated male in acute delirium, with hallucinations. The liver edge was barely palpable. The blood and spinal fluid Wassermann reactions were negative.

gestion of the liver was found in patients No. 282 and 289. In the latter patient, the passive congestion was recent and slight. In the former, marked sclerosis around the central vein, resulting from cardiac decompensation over a period of two years, caused no alteration in the excretory function of the liver. This case suggests that the excretory function of the liver need not necessarily be altered, even in advanced congestive heart failure. In patient No. 303, terminal focal necroses of the liver were found.

#### DISCUSSION OF RESULTS

Pathological retention of Rose Bengal dye in dis-

TABLE III  
Neoplasms of the Liver

| Case No. | Clinical Diagnosis                | Icterus Index | Rose Bengal Test |         | Pathological Diagnosis                            | Origin of Material |
|----------|-----------------------------------|---------------|------------------|---------|---------------------------------------------------|--------------------|
|          |                                   |               | 8 min.           | 16 min. |                                                   |                    |
| 147      | Metastatic carcinoma              | 15            | 60%              | 40%     | Metastatic carcinoma (gastric)                    | Autopsy            |
| 153      | Metastatic carcinoma (Esophageal) | 4             | 50%              | 20%     | Metastatic epidermoid carcinoma                   | Biopsy             |
| 164      | Metastatic carcinoma (gastric)    | 18            | 60%              | 50%     | Metastatic carcinoma (gastric)                    | Autopsy            |
| 178      | Monocytic leukemia                |               | 56%              | 30%     | Monocytic leukemia; infiltration of portal trunks | Autopsy            |
| 326      | Metastatic carcinoma              | 38            | 52%              | 66%     | Primary hepatic endothelioma                      | Autopsy            |

Urobilinogen by the Wallace and Diamond test (1) was present in the urine in 1:30 dilution. The icterus index was 15, and the Rose Bengal test was normal. The patient's condition became rapidly worse, and he expired after 14 days. At autopsy, there were no important findings. The liver showed no pathologic alteration.

In several others, as noted in Table IV, the following abnormalities were present: A terminal disseminated tuberculosis in patient No. 251, which probably had not been present four months before death when the test had been performed. Chronic passive con-

cases of the liver, without jaundice, is seen only in the presence of diffuse intrahepatic lesions. Moreover, retention of the dye is apparently proportional only to the degree of structural change of the hepatic parenchyma. Therefore, types of hepatic lesions cannot be differentiated by this test.

Complete obstruction of the common bile-duct produces a high icterus index and a marked degree of dye retention. The latter increases with the duration of the block, indicating that distortion of hepatic parenchyma and possibly injury to the local components of the reticulo-endothelial system also plays a part. In

TABLE IV  
Extrahepatic Diseases

| Case No. | Clinical Diagnosis                         | Icterus Index | Rose Bengal Test |         | Pathological Diagnosis                                                                 | Origin of Material |
|----------|--------------------------------------------|---------------|------------------|---------|----------------------------------------------------------------------------------------|--------------------|
|          |                                            |               | 8 min.           | 16 min. |                                                                                        |                    |
| 198      | Alcoholic delirium                         | 15            | 56%              | 36%     | Normal liver                                                                           | Autopsy            |
| 240      | Anemia, undetermined etiology              | 11.5          | 80%              | 51%     | Normal liver                                                                           | Biopsy             |
| 251      |                                            |               |                  |         |                                                                                        | Autopsy            |
| 282      | cardiac failure                            |               |                  |         |                                                                                        | Autopsy            |
| 289      | Syphilitic heart disease with pericarditis |               | 53%              | 29%     | Syphilitic pericarditis with slight passive congestion                                 | Autopsy            |
| 297      | Addison's disease                          |               | 58%              |         | Idiopathic atrophy of adrenals                                                         | Autopsy            |
| 303      | Thrombophlebitis                           | 13.5          | 51%              | 32%     | Generalized atypical thrombophlebitis obliterans; terminal focal necrosis of the liver | Autopsy            |
| 364      | Undiagnosed                                |               |                  | 25%     | Normal liver with calcified scar                                                       | Biopsy             |



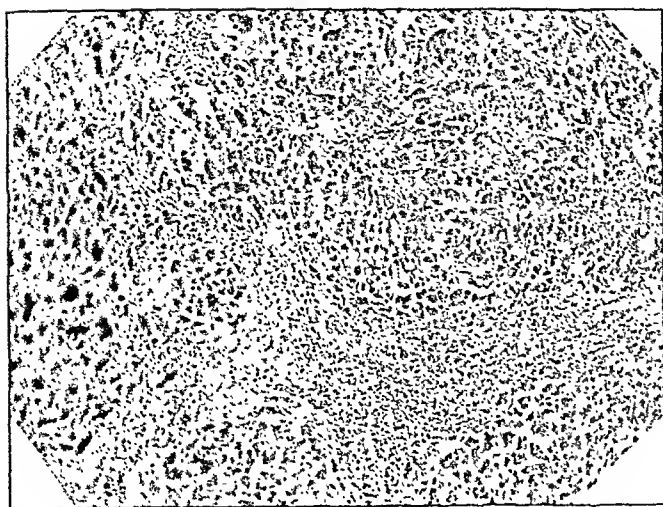


Fig. 4

patient No. 58, following a prolonged obstruction of the common duct, the retention of the dye increased, in spite of the fact that the block had been released in the interim, indicating secondary parenchymatous damage which was verified at autopsy. Photomicrograph No. 7 shows details of the liver in this case. This indicates how intimately biliary obstruction is related to parenchymatous damage, and explains why extrahepatic and intrahepatic block cannot be differentiated by liver function tests except immediately after onset, and then only by means of tests based on the metabolic activity of the liver.

Neoplasms of the liver which do not obstruct the bile-ducts, may cause no abnormality in the excretory function. Neoplasms impinging on intra—or extra-hepatic bile-ducts cause retention of the dye, and jaundice, in proportion to the degree of obstruction. This parallelism between the icterus index and the Rose Bengal test was already pointed out in the analysis of clinical results.

Among the 29 patients who had a Rose Bengal test and a histological examination of the liver, only one, a case of severe anemia, showed the combination of pathological dye retention and normal hepatic parenchyma. Among the same patients, only one, a case of severe chronic passive congestion, had a negative Rose Bengal test in the presence of structural changes in the liver. There was, thus, a 93 per cent agreement between the dye excretion test and the pathological examination. The modified glucose tolerance test was performed with positive results in 8 patients of this series, and in every case anatomical disease of the liver was present.

#### AN EVALUATION OF THE USEFULNESS OF LIVER FUNCTION TESTS

The study of hepatic function for clinical purposes occupies a rather unique position: After investigations extending over a period of about 40 years, the clinical usefulness of liver function tests has been neither generally accepted or universally rejected. The same statement applies in an even greater measure to individual tests of hepatic function. One of the reasons for such a conflict of opinions is that the aims

Fig. 4. (Case No. 64, Table 1). Liver from a patient with early biliary cirrhosis. The section shows distortion of hepatic parenchyma due to inflammatory reaction in and around the portal spaces. X 100.

and limitations of functional examination of the liver are often not completely realized.

The primary object of hepatic function tests is to detect the presence of functional insufficiency of the liver and to measure its degree. Even an ideal liver function test is not suitable for determining the *cause* of hepatic insufficiency, except by deduction, and therefore should not be expected to furnish diagnoses. Moreover, as amply demonstrated in our first paper, the presence of impaired hepatic function does not necessarily indicate the existence of a primary disease of the liver. Neither does a negative outcome of one or several liver function tests always mean absence of hepatic disease.

Functional testing of the liver has been of service in three respects: 1. In supplementing other methods of studying patients with known or suspected diseases of the liver; 2. In revealing the presence of secondary hepatic insufficiency in a variety of extrahepatic diseases in which formerly no such involvement of the liver was suspected. Consequently our understanding of the pathological physiology of these diseases has been enhanced; 3. As an important safety-measure before certain potentially dangerous therapeutic procedures are instituted. Among these are particularly cholecystectomy (2), thyroidectomy, major surgical operations in the presence of hepatic disease (3), and the administration of arsenicals in syphilis (4). When the existence of considerable hepatic insufficiency is established, conservative treatment or appropriate pre-operative preparation consisting of a period of glucose therapy (5), will avert or minimize dangerous or even fatal consequences.

For correct interpretation of liver function tests in hepatic disease, it is of utmost importance to consider the bearing which the probable type and extent of the pathological process will have on any given test. Early damage to the liver may cause irritation and hyperfunction, instead of hypofunction to any test. Vigorous regeneration of hepatic parenchyma during convalescence from acute diseases, or in remissions of chronic ones, is likely to mask the extent of involvement when



Fig. 5

Fig. 5. (Case No. 72, Table 1). Liver from a patient with Banti's syndrome. The section shows perilobular fibrosis. X 100.



Fig. 6. (Case No. 252, Table 1). Liver from a patient with thrombosis of the portal vein. The section shows irregular zones of scar tissue scattered throughout the liver. X 100.

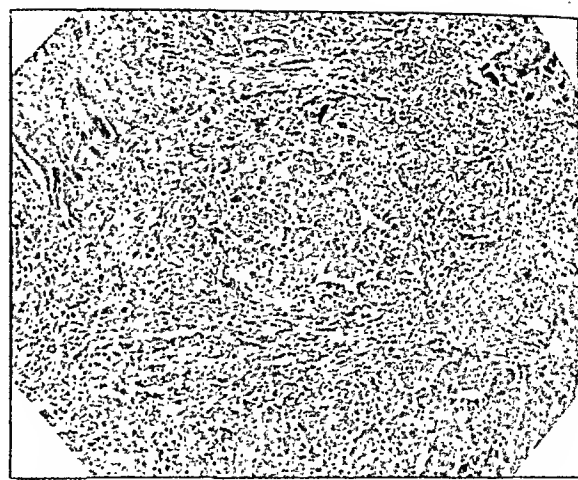


Fig. 7. (Case No. 58, Table 1). Liver from a patient with biliary cirrhosis. The section shows extensive portal scarring with bile-duct proliferation. X 100.

a metabolic test is used. Under the same conditions, due to a lag in the re-establishment of proper biliary drainage, the degree of hepatic insufficiency will be exaggerated if an excretion test is employed. Obstruction of the common bile-duct interferes immediately with tests of excretion, and after about a week begins to influence adversely metabolic tests by causing genuine parenchymatous damage. All liver function tests are much more responsive to diffuse involvement of the whole liver, even when slight, than to complete destruction of considerable portions of this organ if the remaining hepatic tissue is normal. Illustrations of this are found in patients with abscesses, cysts, and tumors which do not involve large bile-ducts. This peculiarity is explained not only by the extraordinary capacity of the liver to regenerate its substance, but also by the fact that, much like renal glomeruli, some of its functional units are normally resting and can be mobilized in case of necessity.

It is evident that extrahepatic conditions which may cause secondary insufficiency of the liver must be taken into consideration when a patient is investigated for the presence or degree of a primary hepatic disease. This, as can be seen from our data, is the greatest potential source of error, since the number of negative tests in the presence of hepatic disease is small. Dye excretion tests are influenced by the condition of the reticulo-endothelial system. The changes in the excretion of Rose Bengal caused by splenectomy and splenomegaly are a case in point. Most metabolic functional tests depend, in addition to the amount and state of hepatic parenchyma, on the activity of other organs concerned with the particular phase of metabolism. This is especially evident when various carbohydrate tolerance tests are utilized. An instance of this kind is the invalidity of the modified glucose tolerance test in hyperinsulinism.

In regard to quantitative measurement of hepatic insufficiency by liver function test, it is our opinion that the terms "slight," "moderate," and "advanced" represent the limits of accuracy. Finer distinctions, except perhaps in following the progress of the same patient, are not justified.

In the choice of a liver function test, it is well to consider that the liver possesses a number of different

functions, and that it should not be extremely difficult to work out a set of conditions under which the efficiency of one of these functions can be put to test. Consequently, it is reasonable to expect that almost any of the more commonly employed liver function tests would be useful clinically. On the other hand, there is little basis for hope that such tests, present or future\*, will prove to be free from the enumerated limitations. For this reason, it is wise in most cases not to rely exclusively on a single test, but to select one excretion and one metabolic test, and to work with them until sufficient familiarity is acquired to know what can be expected from each. Since, under ordinary physiological conditions, the amount of functioning tissue in the liver is constantly changing, tests which determine hepatic capacity during periods of induced maximum activity, are to be preferred. Tests of this type impose a "load" on the liver, as distinguished from tests which measure a normal metabolite.

In our own work, the Rose Bengal test has proven itself to be a simple, inexpensive and satisfactory excretion test. The modified glucose tolerance test, while more time-consuming and more expensive, has rendered good services as a supplementary metabolic test.

We feel that if the proper uses and inherent limitations of liver function tests were more often stressed in the literature, fewer physicians would see their exaggerated hopes disappointed, and the study of hepatic function for clinical purposes would soon settle into its proper place in medicine.

\*There is reason to believe that roentgenological visualization of the liver by means of thorium salts, if shown to be safe, will to a large extent, replace liver function tests in the diagnosis of many diseases of the liver, just as the gastro-intestinal series has limited the scope of gastric analysis. This is due to the fact that physiological tests of hepatic function measure the performance of the liver as a whole, whereas visualization of opaque salts incorporated in the Kupffer cells reveals localized destruction of even relatively small areas of parenchyma.

#### REFERENCES

1. Wallace, J. B., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function. *Arch. Int. Med.*, 35:698, 1925.
2. Smithies, F.: Discussion of Paper by Piersol, G. M., and Rothman, M. M.: Practical Value of Liver Function Tests. *J. A. M. A.*, 91:1768, Dec. 8, 1928.
3. Robertson, W. E.; Swalm, W. A., and Konzelmann, F. W.: Functional Capacity of the Liver. *J. A. M. A.*, 99:2072, Dec. 17, 1932.
4. Biskind, G. R.; Epstein, N. N., and Kerr, W. J.: Hepatic Complications in the Treatment of Syphilis. *Ann. Int. Med.*, 7:265, 1934.
5. Althausen, T. L.: Dextrose Therapy in Diseases of the Liver. *J. A. M. A.*, 100:1163, April 15, 1933.

# ABSTRACTS

VIRGIL H. MOON.

"*Experimental Cirrhosis in Relation to Human Cirrhosis*" General Review—*Arch. Path.* 18: 381-421, Sept., 1934.

The very extensive literature upon experimental portal cirrhosis is reviewed by the author. He, as well as many other workers in this field, emphasize the fact that destruction of the lobular, architectural pattern of the liver is the most characteristic feature of portal cirrhosis in man. The author, therefore, insists upon this definite loss of lobular architecture as the essential differential criterion in determining whether any particular type of experimental cirrhosis simulates portal cirrhosis in man. This survey indicates that a number of agents, very diverse in character, are capable by repeated action, of causing this characteristic picture of experimental portal cirrhosis. The latter condition results from necrosis of hepatic cells, followed by regeneration of local patches or nodules of liver cells, with proliferation and subsequent contraction of fibrous tissue. In many of these cases, the characteristic obstruction of the radicles of the portal vein has been noted. The agents referred to above include various chemicals, (such as phosphorus plus alcohol, manganese chloride plus phenylhydrazin, and carbon tetrachloride), tars, foreign proteins, decomposition products of proteins, infections, immune sera, etc. Certain combinations of agents are frequently more effective in producing experimental portal cirrhosis than are the individual agents.

The belief that portal cirrhosis is caused directly by alcohol has not received experimental support. Alcohol alone is incapable of producing necrosis of the hepatic cells, and this is the essential first step in the development of a portal cirrhosis. On the other hand, there is convincing, experimental evidence to indicate that alcohol does act as a contributing, or aggravating, factor in the development of Laennec's cirrhosis, when it is combined with other agents capable of producing necrosis of liver cells. For example, when alcohol is used to supplement the effect of infection, phosphorus, chloroform, or carbon tetrachloride, the resulting cirrhotic changes are more marked than those resulting from the latter agents alone. This is probably due to the fact that alcohol does produce degenerative changes in the liver cells, which render the cells more susceptible to necrosis by the supplementary agent employed.

The conviction that low grade infection is an important factor in the causation of cirrhosis in man has become rather general among pathologists. Experimental portal cirrhosis has been produced in animals by repeated subcutaneous injections of putrefactive bacteria. Cirrhosis has also been produced by the repeated injection of attenuated cultures of staphylococci. The importance of a low virulence of the infecting organism has been emphasized by several workers. In an epidemic of cirrhosis among cattle, resembling portal cirrhosis in man, coccoid organisms were cultured from the livers. The same organism, when injected into rabbits, produced marked necrosis of the liver cells with early death of the animals before cirrhotic changes could occur.

There is also evidence that metabolic disturbances may be important contributing factors in the development of cirrhosis. In this connection, there is considerable evidence to suggest that hyperthyroidism may contribute to the development of cirrhosis by producing a low glycogen content of the liver. It is known that livers with a low glycogen content do have an increased susceptibility to injury.

In conclusion, the author feels that "A survey of experimental and clinical studies on cirrhosis convinces one that no single causative factor is responsible. Cirrhosis is synonymous with chronic, progressive hepatitis. Its etiology will be found to be as variable as are the agents which, singly or in combinations, may cause chronic, diffuse, progressive inflammation of the liver".

John G. Mateer, Detroit.

MACLAGAN, N. F.

*The Test-Meal in the Diagnosis of Gastric Disease.* *Lancet*, 227, Sept. 1, 1934, 471-475.

The present paper gives the results of an attempt to compare the different types of test-meal now in use, and to assess the value of each on the basis of some of the statistics which recently have been published.

All recent papers have been confined to a tabulation of the degree of acidity in the normal and diseased stomach and it is on this basis that the comparison is made. Working out the statistical probabilities from the percentage acidities in Marks' and Kantor's series of 1800 cases given the Ewald test meal no diagnostic information is gained if the question is one of peptic ulcer and similarly if the diagnosis rests between peptic ulcer and gastric carcinoma. If the question is simply one of malignancy 23.5 per cent instead of the real 22.5 per cent of cases will be diagnosed as gastric cancers, that is in the presence of achlorhydria. In applying the same methods to the same cases but using the figures obtained from Koyihar's series of 450 cases of fractional analysis the same results are gained. When however these methods are applied to Poland's series of 988 cases of histamine tests the results much more information is gained. Histamine gives useful information in 14.9 per cent of cases of doubtful peptic ulcer. It is of no use as a means of discriminating between peptic ulcer and gastric cancer. It gives useful information in 78.5 per cent of cases of doubtful carcinoma of the stomach.

John J. Day, Montreal.

FRIEDENWALD, JULIUS AND FELDMAN, MAURICE.

*The Unstable or Irritable Duodenum: Clinical Observations in One Hundred Cases.* *Journal of the A. M. A.*, 103:2007, Dec. 29, 1934.

The unstable or irritable duodenum, like the unstable colon, results from neuromuscular imbalance.

Disturbed duodenal motility may result from mechanical, chemical, allergic, nervous or reflex causes.

Males predominate in the group of cases studied.

The symptoms may simulate duodenitis, duodenal ulcer, cholecystitis, appendicitis or other abdominal disorders. Abdominal pain is unusual. The bowels are constipated. Symptoms occur in attacks with interval periods of good health.

Diagnosis is suggested by the history of headache, dizziness, insomnia and exhaustion in a high strung individual. The gastric analysis may reveal a hyperchlorhydria. The roentgen evidence obtained by fluoroscopy of the irritable bulb is increased motility, transient irregularities and fibrillation noted along the borders, transient spasm, tenderness over the duodenum and absence of ulcer filling defect.

Treatment is based on the use of an acid free bland diet of high caloric content. Absolute rest in bed is advocated in the beginning. When hyperchlorhydria is present, alkalies should be used. Belladonna and atropine are useful to allay spasm.

Francis D. Murphy, Milwaukee.

## SECTION II—*Experimental Physiology*

### Decompression of the Obstructed Biliary System in the Cat\* II. Serum Bilirubin Concentration and Bromsulphalein Retention

By

ABRAHAM CANTAROW, M.D.

HAROLD L. STEWART, M.D.

and

STANLEY G. McCOOL, M.D.

PHILADELPHIA, PENNSYLVANIA

THE materials and methods employed in this study have been described previously (1, 2). Estimations of serum bilirubin concentration and bromsulphalein retention were made at varying intervals during total stasis and following removal of the ligature on the common duct. Bromsulphalein was injected in the dosage of 2 mg. per kilogram of body weight and the figures reported represent the degree of retention at the end of 30 minutes. Serum bilirubin was determined by the Van den Bergh method as modified by Thannhauser and Anderson. All animals were excluded from the present report in which any complicating factor was present. Sections of liver were removed at the time of operation for removal of the ligature on the common duct for the purpose of comparing the histologic features of the liver of stasis with those of the liver of decompression in individual cases. The data presented herewith, therefore, represent the changes in serum bilirubin concentration and bromsulphalein retention during uncomplicated total bile stasis and uncomplicated subsequent decompression of the biliary system in 17 cats, in 11 of which cholecystectomy had been performed at the time of ligation of the common duct.

#### EXPERIMENTAL OBSERVATIONS

##### *Serum Bilirubin Concentration:*

The serum bilirubin values during stasis and decompression are presented in detail in Table 1. Although there was marked individual variation in the degree of bilirubinemia during stasis, the findings in the animals with gallbladders and patent cystic ducts did not differ essentially from those in which cholecystectomy or cystic duct ligation had been performed. The direct Van den Bergh reaction was positive in every case in which bilirubin could be detected in the blood serum. The concentration tended to reach a maximum between the end of the first and the middle of the second week of stasis.

The following changes in serum bilirubin occurred after removal of the ligature on the common duct:

1. Marked decrease at the end of 24 hours: Cats 63, 87, 121, 122, 125, 128, 129, 131, 132, 143 and 147.
2. Gradual decrease (24-96 hours): Cats 82, 116 and 152.
3. Primary decrease and secondary increase: Cats 63 and 77.
4. Primary increase and secondary decrease: Cat 72.
5. Unchanged: Cat 144.

##### *Bromsulphalein Retention:*

The data regarding the degree of dye retention during stasis and decompression are presented in detail in Table 1. The variation in this factor was even more marked than in the serum bilirubin concentration. An absence of bromsulphalein retention was observed as late as the 15th day of stasis (Cat 128) while 100 per cent retention was noted as early as 24 hours after ligation of the common duct (Cat 87).

The following changes occurred after removal of the ligature from the common duct:

1. Marked decrease at the end of 24 hours: Cats 63, 87, 121, 122, 125, 129, 132, 143, 147 and 152.
2. Gradual decrease (24-96 hours): Cats 82 and 116.
3. Primary decrease and secondary increase: Cats 63 and 125.
4. Increase: Cat 77.
5. Unchanged (no retention): Cats 128, 131 and 144.

#### DISCUSSION

##### *Serum Bilirubin Concentration:*

Cantarow and Stewart (1) have pointed out the fact that no morphological basis can be demonstrated for the marked degree of individual variation in serum bilirubin concentration during total bile stasis. No correlation could be established between the degree of bilirubinemia and the occurrence or extent of regressive and regenerative changes in individual cases. Their observations seemed to indicate that there is no demonstrable correlation between the structural changes in the liver and bile ducts and the variability

\*From the Laboratory of Biochemistry, Jefferson Hospital, the Laboratories of Pathology, Jefferson Medical College and Hospital and the Jefferson Hospital Tumor Clinic.

Submitted January 26, 1935.

in serum bilirubin concentration during the period of total stasis. It was also noted, as in the present series, that after ligation of the common bile duct the rather rapid initial rise in serum bilirubin is followed by a fall to a comparatively low level. The possible dependence of this phenomenon upon anemia, diminished activity of hemoglobin regeneration and suppression of bile acid synthesis was discussed in a previous communication (1).

Clinical observations upon patients following operative or spontaneous relief of common duct obstruction indicate that in the majority of cases which terminate favorably the serum bilirubin concentration falls to normal promptly or within a relatively short time. Similar findings were reported by Snell, Greene and Rowntree (3) and by Armstrong (4) in a few observations made upon dogs. In the present series, a marked decrease in the degree of bilirubinemia occurred within 24 hours in 11 animals following relief of total stasis of 1-16 days' duration. In these cases (Cats 63, 87, 121, 122, 125, 128, 129, 131, 132, 143 and 147) the architectural distortion which constituted one of the most prominent features of the liver of decompression was present to only a relatively slight degree. Only two of these animals (63 and 131) fell into the group in which stasis had existed for 6-10 days, the group in which the subsequent disturbance of architectural pattern appeared to be most marked. Furthermore, in one of these (121) this feature was not pronounced and in the other (63) the serum bilirubin, which decreased during the first 24 hours of decompression, exhibited a secondary increase during the second day, associated apparently with complete suppression of bile secretion. There was much less uniformity in the extent of regressive changes in the hepatic parenchyma in this group. In three instances (87, 121, 132) there was a distinct diminution in the extent of sporadic and focal necrosis and improvement in the appearance of the subcapsular zone (after 7 days decompression in Cat 87); in two cases (131 and 143) there were definitely increased degeneration and necrosis generally throughout the parenchyma, being very marked in Cat 131, in which only about 20 per cent of the hepatic cell nuclei were visible. In two additional cases (128 and 147) degenerative changes in the subcapsular area were increased although the remainder of the parenchyma seemed to be recovering from the effects of stasis. Although some evidence of hepatic cell regeneration, including mitotic figures, binucleation, nuclear hyperchromasia and the presence of characteristically new hepatic cells, was noted in every animal in this particular group, these features were extremely inconstant and variable in degree, bearing no apparent relation to the clinical condition of the animal nor to the extent of fall in serum bilirubin concentration. The same was true of pigmentation and changes in the Kupffer cells and proliferated bile ducts. Bile was present in the intestine and ducts in each case, was of thin consistency and varied in color from light brown to dark green.

In Cats 63 and 77, a primary fall in serum bilirubin was followed by a rise during the second day of decompression. In the latter case the final value, 2.24 mg. per 100 cc., exceeded any obtained in that animal during stasis. There was only slight architectural distortion and relatively slight regression of the proliferated bile ducts which were exceedingly numerous, practically completely surrounding each lobule. Hy-

aline necrosis was rather extensive. Although mitotic figures were scarce there was other evidence of regeneration of hepatic cells, certainly not less than in animals in which the serum bilirubin fell promptly following relief of obstruction. The bile ducts were patent and thin brown bile was present in the intestine and ducts. In Cat 63, in which there was apparently complete suppression of bile secretion, there was a definite increase in the degree and extent of the regressive changes in the hepatic cells and also marked architectural distortion. On the other hand, mitotic figures were exceedingly numerous and there were other striking indications of active hepatic cell regeneration. The secondary increase in the degree of bilirubinemia in this case, however, may have been dependent in part upon the fact that thrombosis had occurred in several branches of the portal vein.

In the three cases in which the serum bilirubin diminished gradually (Cats 82, 116 and 152), the degree of architectural disruption varied from slight (116) to moderate, and degenerative changes in the hepatic cells were equally variable. A marked feature in Cat 116 was the extreme degree of disarrangement, loosening and edema of the connective tissue about the larger intrahepatic bile ducts. Active regeneration of hepatic cells was noted in each instance, being particularly marked in Cat 82, in which 2 mitotic figures could frequently be seen in single high-power fields; thrombosis of branches of the portal vein were present in this case.

In Cat 144, in which no change occurred in the serum bilirubin concentration (0.0 mg.), the liver showed increased degeneration and necrosis, moderate disruption of architectural pattern and slight evidence of hepatic cell regeneration, no mitotic figures being noted. In Cat 72, which exhibited a primary increase in bilirubinemia and a secondary fall, morphological studies unfortunately were not made at the time of the increase in serum bilirubin.

These detailed histologic studies fail to establish any consistent correlation between the very striking morphological features of the liver of decompression and the variable changes which occurred in the serum bilirubin concentration following relief of biliary stasis. The rapidity of fall of the serum bilirubin and the development of increased bilirubinemia apparently were independent of and entirely unrelated to the extent of architectural, regressive or regenerative changes in the hepatic parenchyma and to changes in the bile ducts. Changes in the serum bilirubin were also unrelated to changes in the lipid content of the hepatic and Kupffer cells which was studied in detail and which will be described in a subsequent report.

#### *Bromsulphalein Retention:*

Cantarow and Stewart (1) found that during complete bile stasis in cats there was no apparent relationship between the degree of bromsulphalein retention and the morphological changes in the liver and bile ducts, either in individual cases or in the group of animals as a whole. The range of individual variation in the degree of dye retention was even more marked than in that of bilirubinemia and was not consistently related to the duration of stasis. The data presented in Table 1 illustrate the lack of correlation between the degree of bilirubinemia and of bromsulphalein retention during the period of stasis in the animals included in the present study. Cantarow and Stewart (1) discussed the possible causes of the vari-



ability of dye retention which may be dependent upon several variable factors, including destruction, storage or extrahepatic elimination of the dye.

Clinical observations upon patients with obstructive hyperbilirubinemia indicate that following relief of the obstruction to the flow of bile, the degree of dye retention, although diminishing, usually persists for a variable period of time after the serum bilirubin concentration has returned to normal. This has been attributed to the residual hepatitis which is present in nearly all individuals who have suffered from biliary obstruction for an extended period. In a few observations upon dogs, Snell, Greene and Rowntree (3) found that bilirubinemia and dye retention decreased simultaneously following the re-establishment of bile flow and they concluded that the two phenomena are distinctly related.

In the present series of animals, a marked decrease in the degree of bromsulphalein retention was present at the end of 24 hours following relief of obstruction in 10 instances (Cats 63, 87, 121, 122, 125, 129, 132, 143, 147 and 152), after stasis of 1-16 days duration. With a single exception (152), this was associated with a corresponding fall in the serum bilirubin concentration. In the latter case (152) there was no demonstrable morphological basis for this discrepancy. The hepatic lesions and the changes in the Kupffer

cells differed in no essential respect from those present in the other animals in this group. In Cat 63 the primary decrease in the degree of dye retention and bilirubinemia was followed by a secondary increase in both factors. At the time of this increase (48 hours decompression) the only unusual morphological finding was thrombosis of some of the branches of the portal vein, although both regressive and regenerative changes in the hepatic parenchyma were more pronounced than during stasis. No consistent morphological changes were associated with the prompt decrease in dye retention exhibited by this group of animals. The regressive, regenerative, vascular and ductal lesions characteristic of the liver of decompression varied considerably and bore no demonstrable relation to the uniform functional findings in these cases.

A relatively gradual diminution in the degree of dye retention was noted in 2 instances (Cats 82 and 116). In Cat 82, which had appeared quite toxic since the removal of the ligature on the common duct, rather marked regressive changes were associated with evidences of extremely active regeneration of hepatic cells, extensive vacuolization of the bile duct epithelium, marked pigmentation of both hepatic and Kupffer cells and thrombosis of branches of the portal vein, with infarction. In Cat 116 there was extreme

TABLE I

*Serum bilirubin concentration and bromsulphalein retention during biliary stasis and decompression*

| DAYS OF TOTAL STASIS |          |             |             |             |            |           |            |           |            |   |            |            |             |    |    |           | DAYS DECOMPRESSION |             |             |            |          |
|----------------------|----------|-------------|-------------|-------------|------------|-----------|------------|-----------|------------|---|------------|------------|-------------|----|----|-----------|--------------------|-------------|-------------|------------|----------|
| Cat.                 |          | 1           | 2           | 3           | 4          | 5         | 6          | 7         | 8          | 9 | 10         | 11         | 12          | 13 | 14 | 15        | 16                 | 1           | 2           | 3          | 4        |
| †63                  | D*<br>B‡ |             |             |             |            |           | 70<br>1 91 |           |            |   |            |            |             |    |    |           |                    | 25<br>1.05  | 100<br>1.64 |            |          |
| 72                   | D<br>B   |             |             |             |            |           |            |           |            |   |            | 30<br>2 48 |             |    |    |           |                    | 50<br>3.64  |             | 5<br>0.1   | 0<br>1.0 |
| 77                   | D<br>B   | 45<br>0 91  |             | 15<br>1.31  |            | 40<br>1 6 |            |           |            |   | 55<br>0 96 |            |             |    |    |           |                    | 100<br>0 83 | 100<br>2 24 |            |          |
| †82                  | D<br>B   | 30<br>1 24  | 55<br>1 72  | 80<br>2 24  | 60<br>3 16 |           |            | 30<br>6.5 | 100<br>6 S |   |            |            |             |    |    |           |                    | 100<br>4.56 | 20<br>1.67  |            |          |
| †87                  | D<br>B   | 100<br>0 61 | 100<br>1 12 | 100<br>2 16 |            |           |            |           |            |   |            |            |             |    |    |           |                    | 5<br>0 35   |             | 0<br>0.17  | 0<br>0 0 |
| 116                  | D<br>B   |             |             |             |            |           |            |           |            |   |            |            | 100<br>2 92 |    |    |           |                    | 80<br>2.31  |             |            |          |
| †121                 | D<br>B   |             |             |             |            |           |            |           | 60<br>3 18 |   |            |            |             |    |    |           |                    | 10<br>0.68  |             |            |          |
| †122                 | D<br>B   |             |             |             |            |           |            |           |            |   |            | 75<br>4 0  |             |    |    |           |                    | 0<br>1.32   |             |            |          |
| 125                  | D<br>B   |             |             |             |            |           |            |           |            |   |            |            |             |    |    |           | 100<br>3.4         | 0<br>1.36   | 0<br>1.0    | 20<br>1.52 |          |
| †128                 | D<br>B   |             |             |             |            |           |            |           |            |   |            |            |             |    |    | 0<br>1 44 |                    | 0<br>0.72   | 0<br>0.2    |            |          |
| †129                 | D<br>B   |             |             |             |            |           |            |           |            |   |            |            |             |    |    |           | 30<br>2.62         | 0<br>0.82   |             |            |          |
| †131                 | D<br>B   | 0<br>0 68   |             |             |            |           |            |           |            |   |            |            |             |    |    |           |                    | 0<br>0 0    |             |            |          |
| †132                 | D<br>B   | 20<br>2 04  |             |             |            |           |            |           |            |   |            |            |             |    |    |           |                    | 0<br>0.4    |             |            |          |
| 143                  | D<br>B   |             | 35<br>0 74  |             |            |           |            |           |            |   |            |            |             |    |    |           |                    | 0<br>0.0    |             |            |          |
| †144                 | D<br>B   |             | 0<br>0 0    |             |            |           |            |           |            |   |            |            |             |    |    |           |                    | 0<br>0.0    |             |            |          |
| †147                 | D<br>B   |             | 100<br>2 4  |             |            |           |            |           |            |   |            |            |             |    |    |           |                    | 5<br>0.2    |             |            |          |
| 152                  | D<br>B   |             |             |             |            |           | 90<br>1 07 |           |            |   |            |            |             |    |    |           |                    | 50<br>1.14  | 0<br>0.2    | 0<br>0.0   |          |

\*Dye (bromsulphalein) retention expressed as percentage

†Serum bilirubin concentration in milligrams per 100cc.

‡Cholecystectomy.



disarrangement, loosening and edema of the connective tissue about the larger intrahepatic bile ducts. Otherwise, the liver and ducts presented no lesions which differed in any essential respect from those noted in cases in which the degree of dye retention fell promptly following restoration of bile flow.

In Cat 63, a primary decrease in bromsulphalein retention from 70 per cent to 25 per cent (24 hours) was followed by a secondary increase to 100 per cent at the end of 48 hours of decompression. The liver at this time showed marked architectural distortion, increased degeneration and necrosis and evidences of extremely active hepatic cell regeneration. There were thrombosis of several branches of the portal vein and apparently complete suppression of bile secretion, with a slight increase in serum bilirubin and no pigmented bile in the duct system. A sustained increase in the degree of dye retention, from 55 per cent to 100 per cent after 24 and 48 hours of decompression, occurred in Cat 77, accompanied by an increase in the serum bilirubin concentration. With the exception of rather extensive hyaline necrosis, regressive changes were not marked and hepatic cell regeneration was only moderately active. There were only slight architectural distortion and marked proliferation of the smaller bile ducts. No dye retention was noted during the period of decompression in Cats 128, 131 and 144, in which no retention had been present during stasis. Cat 131 showed a very marked degree of sporadic necrosis, only about 20 per cent of the hepatic cell nuclei being visible in histologic sections. Regressive changes were also more extensive than during stasis in Cat 144. Architectural distortion varied considerably as did hepatic cell regeneration. In Cat 128 there was an extreme degree of Kupffer cell vacuolization (fat).

On the basis of these observations, it seems clear that the degree of bromsulphalein retention diminishes rapidly in the majority of cases following the re-establishment of bile flow. In most cases in which it diminished more gradually or actually increased the

morphological changes in the liver differed in no essential respect from those in which it fell promptly. Thrombosis of branches of the portal vein may have been responsible, in part at least, for the findings in Cats 63 and 82. In general, however, it appears that similar changes in dye retention may occur during biliary decompression in animals with widely differing morphological changes in the liver. On the other hand, variable functional findings may be obtained in animals in which histological examination of the liver reveals no significant morphological differences. The same applies to the lipid content of the hepatic and Kupffer cells which will be described in a subsequent report. It is also of interest that, with a single exception (Cat 77), the changes in the degree of bromsulphalein retention approximately paralleled those in bilirubinemia during decompression. This is in sharp contrast to the frequent lack of parallelism of these two factors during total stasis.

#### SUMMARY

1. No consistent correlation could be established between the striking morphological features of the liver of decompression and the changes which occurred in the serum bilirubin concentration following relief of biliary stasis.

2. In the great majority of cases, the serum bilirubin fell promptly following relief of obstruction.

3. In contrast to the findings during total stasis, during decompression changes in the degree of dye retention generally paralleled the changes in bilirubinemia.

4. No consistent correlation could be established between morphological changes and the changes in the degree of bromsulphalein retention during the period of decompression.

#### REFERENCES

1. Cantarow, A., and Stewart, H. L.: *Am. J. Path.* (in press).
2. Stewart, H. L., and Cantarow, A.: *This Jour.*, 2:101, 1935.
3. Snell, A. M.; Greene, C. H., and Rowntree, L. G.: *Arch. Int. Med.*, 36:273, 1925; 40:471, 1927.
4. Armstrong, A. R.; King, E. J., and Harris, R. I.: *Canad. Med. Assn. Jour.*, 31:14, 1934.

## ABSTRACTS

MCGAUGHAN, J.M., M.D.

*The Value of Estimation of the Amylase of the Blood in the Diagnosis of Suspected Pancreatic Disease. S. G. and O., Volume 59, No. 4, Oct., 1934, pp. 598-610.*

In this article a review of the literature on this subject is made and a series of experiments involving various pathological conditions of the pancreas is reported.

In a series of fifteen apparently healthy dogs, blood amylase averaged 24.6 units, the lowest reading obtained was 15 units and the highest was 44.4 units.

These experiments showed that obstruction to the outflow of pancreatic juice which occasioned various degrees

of pancreatitis showed rises in blood diastase values above normal within a very few hours, the maximal rise being reached in about 72 hours and being sustained for from eight to fifteen days. The height of the rise is directly proportional to the degree of occlusion of the pancreatic duct or to the extent of parenchyma involved in the inflammatory process. Following this initial rise in the blood diastase after about two weeks the curve gradually returned to normal.

The author feels that this test may be very valuable in the detection of pancreatic disease, but points out that its value lies in the early stages of the disease.

N. W. Swinton, Boston.

## SECTION III—Nutrition

### Clinical Evidence of Fifty So-Called Gastrointestinal Diseases Which Really Are Caused by Food Allergy With Discussion of Their Treatment\*

By

JOSEF S. SMUL, M.D.  
NEW YORK CITY, NEW YORK

IN order to present clinical evidence of gastrointestinal food allergy we take as our problem the patient who is frequently "conscious" of his digestive tract. We contend, and will endeavor to prove, that the vast majority of these patients are born with an alimentary tract which is "sensitive" to certain normal foods, or to certain normal cleavage products, derived during normal digestion or to both. (1) This phenomenon is known as "allergy" and is responsible for about fifty clinical syndromes which now are described as individual gastrointestinal "diseases" in all standard text books.

Three sources must be examined in order to find the cause of all forms of distress of the alimentary tract. For this reason, it is best to separate the diseases causing distress in the alimentary tract, according to the sources of the *etiologic irritants*, into three groups:

*Alimentary Group A.* represents that gastrointestinal malfunction which is caused by irritants whose source is *outside* the body, as happens with allergic foods. This affection with its protean symptomatology, can be prevented or controlled by eliminating the allergic foods from the daily diet.

*Alimentary Group B.* represents those gastrointestinal "diseases" which are caused by irritants whose source is *in* the alimentary tract: Diverticula, Carcinoma, Appendicitis, Acute Bacterial Gastrointestinal Intoxication, Bacillary Dysenteric Colitis, Amebic Dysenteric Colitis, Tuberculous Enterocolitis, Amyloid Disease, Chronic Plumbism, Megacolon, Intestinal Parasites.

*Alimentary Group C.* represents those gastrointestinal diseases which are caused by irritants whose source is *outside* the alimentary tract, but *in* the body: Diseases of the Liver and Gall Bladder (tumors, cysts, amyloid); Diseases of the Pancreas (tumors, cysts); Diseases of the Nervous System (migraine, lues, tumors, neurasthenia and other nervous and psychic derangements); Diseases of the Blood (pernicious anemia, leukemia, lymphatic anemia, splenic anemia); Diseases of the Endocrine Glands (hyperthyroidism,

diabetes, hypoparathyroidism); Diseases of the Heart (especially those accompanied by decompensation); Diseases of the Lungs (tuberculosis, pleurisy, tumors); Diseases of the Kidneys (nephritis, pyelitis, tumors, cysts, stones); Diseases of the Genital Organs (tumors, cysts, inflammation, ectopic); Hypertension.

#### ALIMENTARY GROUP A.

Since we are mainly interested in the fifty so-called alimentary "diseases" described in standard text books with only theories or suggestions as to cause and cure, we will consider first *Alimentary Group A*. In conformity with our suggested nomenclature personally we call the digestive disorder embracing what now are fifty separately described diseases, "Alimentallergy".

We will now endeavor:

(1) To show the etiology of the generally considered fifty gastrointestinal "diseases". (2) To induce proof that all these fifty separately described "diseases" are only different groups of symptoms of one disease, "Alimentallergy". (3) To show a method of preventing and neutralizing the evil effects of this malfunction. (4) To show the discovery of a method which obviates the customary routine of testing each patient for each allergic food. (5) To show a method whereby all cathartics and enemas may be omitted in the treatment of this affection, from which suffer nine-tenths of all who require artificially produced bowel evacuations.

#### DEFINITION

Alimentallergy is a condition of the gastrointestinal tract, characterized by an *inborn* sensitiveness to certain normal foods, or to certain normal digestion cleavage-products formed during normal digestion or to both.

#### ETIOLOGY

The cause of this disturbance is an inborn sensitiveness of the alimentary tracts of these patients either to certain normal foods, or to certain cleavage products derived during normal digestion, or to both. In 1922, backed by an extensive experience with gastrointestinal patients, sufficient reasons appeared to warrant suspicion that "food allergy" was the cause of their distress. Many of the following observations led

\*Read (abbreviated) before the New York Physicians-Yorkville Med. Soc. in New York.  
Submitted December 4, 1934.

1. Smul, Josef S.: Gastrointestinal Diseases and Food Allergy. *Med. Jour. and Record*, January 20, 1932.

to this conclusion. It should here be emphasized that although not all the allergic characteristics enumerated below readily can be demonstrated in each of the fifty "diseases" constituting alimentallergy, enough can be demonstrated to prove the allergic nature of each.

### PROOF OF THE ALLERGIC NATURE OF ALIMENTALLERGY

#### 1. *Sudden Onset And Sudden Cessation Of Distress.*

We have been impressed by the sudden onset and sudden cessation of the distress of this affection. Such features are characteristic of anaphylactic conditions. The attack is apt to appear suddenly, last for some time, disappear, and then reappear after an appreciable period of comfort. Most patients are able to assign a cause for the attack. Since they were able to tell approximately when an attack began, they would recall what, to them, produced the upset. One would assign the cause to food eaten at a banquet, the other at a funeral; one would blame the restaurant, the other would blame the cook; one would attribute it to solids, the other to liquids.

If we examined these supposed causes, we would find that the same patients really had been to many banquets and to many funerals without experiencing attacks. Often they had eaten in the same restaurants, or had had the same cook without experiencing any distress. They had eaten the same solids and the same liquids without any ill effects. Indeed, the similarity of these statements to those made by patients with asthma is striking: the asthma patient slept in the same bed and used the same clothing or food for a long time without any trouble: then, suddenly, he developed an attack of asthma. In these cases the explanation offered as the variable factor was a "cold". The patient always could tell *when* the cold came, although he could not tell *how* it came. Nevertheless, he was satisfied to call it a "cold". Then came the knowledge of allergy to explain the cause. Since the liability to an attack depends upon a certain degree of sensitiveness, the patient was able to tolerate the allergic materials during the desensitized period. As soon as his sensitiveness reached a certain degree of excitability, he developed an "attack", should he come into contact with the allergic substance.

Exactly the same condition would seem to operate in the gastrointestinal tract. The patient may eat the allergic foods during the "desensitized" period without any trouble. As soon as he becomes "sensitive" he experiences an attack of alimentary distress, if he eats the allergic materials.

2. *Sensitiveness to Small Amounts of Certain Commonly Used Foods.* We have noticed that some of our patients were, at times, sensitive to such small amounts of certain commonly used foods that the consequences could only be explained by allergy.

*Practical Method of Testing Food Sensitiveness.* From the daily foods, a certain number was selected and from this number our gastrointestinal patients were allowed to eat and drink of them as much as they liked. Also they could choose their own time and manner of eating. But they were not allowed to take any other food and they were compelled to eat of each food allowed at least once a day. If they had no distress they were directed to return for observation in a week. If they were distressed they were asked to report at the end of the day. If the patient reported that he had distress, we endeavored to deduce from

the relation in time between the ingestion of the food and the appearance of pain or discomfort which of the food materials was most likely to cause his distress. The patient was instructed to omit the questionable food from his diet, and advised to eat more of the remaining foods. Occasionally the original selection of prescribed foods in the case became exhausted and a new list had to be prescribed. When the patient had been comfortable for some time, he was retested on each food which had been removed from the original group, to make certain which substance it was which he could not tolerate. In that way the allergic material was discovered. The knowledge thus acquired, enabled us to precipitate an allergic attack or prevent one at will.

The facts stated above also proved that it was not the *amount* of food, nor the *time* or *manner* of eating, which disturbed the patient. The patient who became deathly sick from a spoonful of a certain food, was able to tolerate twenty times as much of another food. The same disturbing food might be taken in quantities twenty times as large by a non-sensitive person, without any ill effects.

(3) *Gastric Acidity.* For many years it was believed that acid, which is a constituent of the normal gastric secretion, was the cause of all forms of gastric disturbance, especially the periodic pain which occurs with or without peptic ulcer. Lately, it has been found that the same type of periodic pain also may exist in persons with anacidity, with achylia or after gastrectomy. Furthermore, fractional examinations of the gastric contents show that the pain does not correspond with the period of highest acidity. Also, it is known that when the stomach contents artificially are evacuated or when the patient vomits at the time of the pain, the pain ceases at once, irrespective of whether or not the stomach contents have an acid reaction.

The examination of the gastric contents thus obtained, reveals normal food and normal cleavage products occurring in the process of normal digestion. Yet, on reintroducing these normal contents to the stomach of the same patient, the previous pain soon recurs.

On the basis of the above observations, we feel justified in concluding that the periodic pain is due to certain normal foods, *when it occurs soon after ingestion*. However, if the pain is *delayed*, it would seem to be due to certain normal cleavage products appearing at that time. Both substances may act as allergins in the stomach.

It can be said in regard to gastric acid, that the allergic substance seems more active in its presence than in its absence.

The normal gastric contents found in "alimentallergy" also explain why many patients suffering distress from it for many years, remain well nourished. The only time these patients show a lack of nourishment is when they eat little because they dread distress, when they vomit much of the food they ingest or when they suffer from diarrhea.

(4) *Spasm.* After the abandonment of the acid theory, the spasm theory was advanced to explain the abdominal pain.

Dr. Hitzenger (2), at the Wenkebach Clinic of Vienna, instructed his nurses to notify him immedi-

2. Hitzenger, K.: Personal communication at the Wenkebach Clinic of Vienna, 1930.

ately when a gastric patient complained of pain. He had everything prepared, and in a few minutes the patient was being fluoroscoped. He observed no different contractions of the stomach or the duodenum than at the previous examination when the patient had been experiencing no pain, even though the pain persisted during the examination being discussed. Dr. Hitzenberger continued these experiments for a considerable period, and concluded that there was no relation between the periodic pain of the stomach or duodenum and any form of spasm. However, on removing the gastric contents from the stomach, as described above under "gastric acidity", the pain ceased.

Thus, there would seem some ground for believing that the only logical explanation is, that the gastric pain is due to certain normal foods or to certain normal cleavage products, which act as allergic substances in the stomach or in the intestines.

(5) *Trauma*. When the traumatic theory of gastrointestinal ulcers was advanced, many experiments had been made in the effort to produce chronic ulcers in animals, similar to those found in man, but without success. The animal's gastric mucosa was damaged, the gastric hydrochloric acid and pepsin were there, but the lesions healed. The explanation would appear to be that the stomachs of the animals are not sensitive to the ingested food. In man, the situation is different. Apparently, a large proportion of humans are born with alimentary tracts which are "sensitive" to certain normal foods which are universally used in the daily diet. Seemingly, it is the *repeated ingestion* of these foods by those with sensitive alimentary tracts which causes and maintains peptic ulcer in man. Alkalies and atropine diminish the allergic activity and thereby produce an amelioration, but they do not remove the cause. However, on withholding from the daily diet those foods which we found to be allergic and feeding the patient on the foods we found to be non-allergic, gastrointestinal ulcers will not develop, or, when present, will heal and not recur, unless the patient resumes the ingestion of the allergic foods.

(6) *Intestinal "Autointoxication"*. There is a group of symptoms causing abdominal as well as general disturbances, which is classed under the term "intestinal autointoxication". This autointoxication is supposed to be produced either by the intestinal mucosa, by improper cleavage of protein during its digestion, or by the usual intestinal bacteria (3). Formerly, it was assumed that this condition occurred especially in those who experienced infrequent bowel movements, and it was taught that assuring regular evacuations would prevent or cure autointoxication. Recently, the contention has been that the autointoxication symptom-complex is more likely to occur when diarrhea is present. The fact is, that those who do not suffer from food allergy do not develop these symptoms whether their bowels move once in five days or five times in one day. But it is a fact also that, if those who *suffer from food allergy* move their bowels more than once a day for any reason, or have a desire to move them more than once a day, invariably they will develop the group of symptoms known as "autointoxication". We observed that if the sensitive patient adhered to the diet rules of food allergy hereinafter described, this group of symptoms does not develop.

In our opinion, what is called "autointoxication" is a fiction.

(7) *Infection*. It is significant that, as far back as infection has been known, many syndromes referable to the digestive system, included in this group, have been laid directly or indirectly at its door. Yet all these claims still are being debated. The present consensus of opinion is that although infection is, in itself, not a primary etiologic factor, it is believed that it may be a contributory cause, even if no positive proof exists to substantiate this suspicion. With so many bacteria always existing in the alimentary canal and the easy accessibility of organisms that enter with the food, it becomes possible to see how infection would suggest itself as a logical causative agent in disease production, but, so far, no one has proved the true relationship, and certain available facts contradict it. The most that can be conceded in this connection is that *after* allergic foods produce damage to the alimentary tract mucosa, certain bacteria then may become virulent, or a group of organisms which ordinarily cannot exist then may enter and contribute to the damage. Evidence to substantiate the last statement may be gathered from the observation that, in some severe cases of colon allergy, the treatment for food allergy is not adequate and autogenous vaccines prepared from bacteria are required. However, in order to secure continuous good results affected patients must adhere to such dietetic restrictions demanded in food allergy, as will be mentioned later.

(8) *Allergic Substances Select Specific Sites*. We observed that allergic substances select not only particular organs or tissues, but also particular sites in the tissue or organ of each individual, which tissue, when "sensitive", always reacts in the same peculiar way.

All are familiar with eczema appearing, disappearing and reappearing in certain individuals, say, on one cheek, behind one ear, over one thigh, or between two fingers on one hand, while the remainder of the skin remains normal. We are also familiar with the particular site the allergic material selects in asthma, or in hay fever. The resulting damage depends upon the amount and duration of the allergic substance on one hand, and upon the degree of sensitiveness and the reaction of the particular tissue in each individual, on the other. It is admissible that an eczema-like lesion situated in the mucous membrane of the stomach or the intestines might become manifest as an ulcer.

Under this conception one logically may explain: (1) the abnormal gastrointestinal motility causing retention, constipation or diarrhea; (2) the alimentary distress of a patient without evident pathology, as in what is now called a simple dyspepsia or a gastric neurosis; (3) the pathology of a hypertrophic or an atrophic stomach or intestine; (4) gastric vascular spasm; and (5) the production, maintenance and selection of a particular site of an ulcer on the lesser curvature of the stomach or the duodenum, including the marked infiltration of eosinophiles, so characteristic of allergic conditions.

(9) *Duke's (4) Proof Of Allergic Cause*. To prove that our position, (as will be emphasized in discussing treatment), fulfills all the requirements necessary to

3. Hewlett, Albion Walter: *Pathological Physiology of Internal Medicine*. D. Appleton and Co., 1928, pp. 204-205.

4. Duke, William W.: *Allergy: Asthma; Hay Fever; Urticaria and Allied Manifestations of Reactions*. The C. V. Mosby Co. 1925, p. 74.

establish the allergic nature of the etiology of affections being considered, the four criteria suggested by Duke are introduced, namely:

(a) If the patient is removed from contact with the suspected substance, he is relieved of symptoms.

(b) If we re-introduce the suspected substance when the patient is well, he has a recurrence of the symptoms *c. g.* as when the patient returns to his previous diet.

(c) If the patient persists in supplying the allergic substances, the tissues will become "exhausted" and cease to react to the suspected substance; this is demonstrated by what are called "spontaneous remissions".

(d) If small amounts of the allergic substances slowly are introduced, the symptoms will cease and a "tolerance" will develop, (see treatment *infra*).

This method of applying directly the *suspected* substance to the *suspected* tissues is called the "direct method" of proving that allergy is the cause, should a reaction follow. It is reliable and is to be preferred to the less reliable "indirect method"; the latter should only be used in cases where the direct method is impractical or impossible.

In inhalatory allergy, it is difficult to apply a definite amount of the suspected inhalent to the affected tissues. Furthermore, serious consequences may follow the use of the direct method in the respiratory tract. Therefore the indirect method, namely *the skin test* is employed.

In gastrointestinal food allergy, the use of the direct method is not difficult. The distress which follows the direct exhibition of offending substances can be controlled readily and no serious consequences appear. Moreover, while there is a considerable relation in the sensitiveness to allergic substances between the skin and the respiratory tract, there is hardly any relationship between the skin and the alimentary tract. Hence the direct method would appear to be the only possible and reliable one to be employed in alimentary food allergy.

Of course the *degree* of sensitiveness of the alimentary tract in allergy varies as does that of the lungs in asthma, or that of the skin in angioneurotic edema. The tissues of these organs sometimes are more sensitive to the allergic substances and, at other times, less. Therefore, frequently we hear that a patient previously has had a similar attack of alimentary distress, but that he has been "cured" and has been well for some time: such a statement frequently is made with respect to all forms of allergy.

#### CLASSIFICATION

It has seemed convenient to divide alimentallergy into six forms; this grouping replaces the following fifty so called "diseases":

(1) *Irritable Alimentallergy*. This form of alimentary tract allergy has no demonstrable pathology and is known only by the distress which it produces. It accounts for the following conditions often considered as diseases: Superacidity, Supersecretion, Gastro-myorrhea, Bulimia, Parorexia, Gastralgokenosis, Gastralgia, Hyperesthesia, Regurgitation, *Eruetatio Nervosa*, *Vomitus Nervosus*, *Nausea Nervosa*, Cardiospasm, Pylorospasm, Pneumatosis, Peristaltic Unrest, Nervous Dyspepsia, Subacidity, Anacidity, Acoria, Anorexia, Sitophobia, Incontinence of Pylorus, Atony, Gastrectasis, Hematemesis (diapedesis), Intestinal Gas Distension, Intestinal Indigestion, Intestinal Colic,

Intestinal Hemorrhage (diapedesis), Constipation, Diarrhea, Infantile Diarrhea, Sprue.

(2) *Acute Inflammatory Alimentallergy*. This type is characterized by an acute transitory inflammation involving the mucosa and replaces the following so-called distinct affections: Acute Gastritis, Acute Enteritis, *Cholera Nostras*, Acute Colitis.

(3) *Acute Suppurative Alimentallergy*. This form of allergy is rare and ends fatally. It is characterized by an acute suppuration of the submucosa and replaces the following conditions: Suppurative Gastritis, Suppurative Enteritis.

(4) *Chronic Hypertrophic Alimentallergy*. This form is characterized by chronic hypertrophy and replaces the following so-called lesions: Chronic Hypertrophic Gastritis, Chronic Hypertrophic Enteritis, Polyposis.

(5) *Chronic Atrophic Alimentallergy*. This form is characterized by chronic atrophy and accounts for: Chronic Atrophic Gastritis, Cirrhosis of the Stomach, Chronic Atrophic Enterocolitis.

(6) *Autolytic Alimentallergy*. This form is characterized by chronic ulcers in the stomach or intestines and replaces lesions considered as disease entities: Gastroduodenal Ulcer, Intestinal Ulcers, Ulcerative Colitis.

#### NOMENCLATURE

The term "alimentallergy" indicates the cause and the site of the disease in conformity with the rules adopted by the International Medical Nomenclature Committee. It is best to omit the old terms because the "diseases", such as they are supposed to represent cannot individually be diagnosed and differentiated from one another during life, by either distinctive etiology, pathology, physical findings, chemical studies, symptoms or treatment. Therefore, the ancient terms are of neither scientific or of practical value.

#### SYMPTOMS

In spite of the fact that the tendency to each particular kind of allergy is inborn, it is characteristic of all forms of allergy that the *manifestation time* varies from the first few days after birth to any time up to the end of life and that all exhibit regressions, remissions and recurrences.

The complaints of the patient in allergic disease are: increased or decreased desire for food, bad taste in the mouth, abdominal distress, fullness in the abdomen, heartburn, eructations, regurgitation, nausea, vomiting, abdominal pain, too frequent bowel movements, inconvenient bowel movements, or blood in the vomitus or stool. Any one or several of these complaints may be present. Distress in various parts of the body may accompany these symptoms: as headache, dizziness, restlessness and fainting spells.

#### DIAGNOSIS

The diagnosis is made by the history of regressions, remissions and recurrences of the above named symptoms, the finding of peptic ulcers with the X-ray or in the rectum by the proctoscope in some patients, the cure of the patient through the mode of management to be mentioned and the previous exclusion of the diseases named in Groups B and C above mentioned.

#### PROGNOSIS

Since allergy is an inborn characteristic which it is impossible to eradicate, one is advised not to use the word "cure" in these cases. However, so long as the



patient will carry out the advice given, he should remain free from symptoms; this is the nearest to cure which it is possible to promise an allergic patient. With this limitation we can promise our patient a 100% cure.

*The causes of failure are:*

(a) The patient does not carry out the treatment properly and adequately.

(b) There exists deformity, as induration, hypertrophy, contraction or adhesions of the alimentary tract, which may have developed from pre-existing ulcers or other organic lesions.

(c) A mistake has been made in the diagnosis. In such circumstances, the cause of the alimentary disturbance is not food allergy and the case does not belong to Group A. The source of the irritant may be a type of intra-alimentary belonging to Group B, or it may be extra-alimentary but within the body, as suggested by Group C.

### TREATMENT

The treatment consists in withholding those foods to which the patient happens to be sensitive and in feeding him foods to which he is not sensitive. At the beginning of our studies, we tested each individual patient for every food, mentioned above under "etiology". However, after testing a large number and then observing them for several years, we noticed that the foods fell into common groups. These we consolidated into one group of foods allowed, called "anallergic foods", and another group prohibited, called "allergic foods". These food lists have been used for a number of years and are perfectly satisfactory. One may state that often the foods to which these patients are sensitive are not essential to life and that the variety of foods which benefits them is so great, that the daily requirements easily are satisfied. The "anallergic foods" also serve as hypo-sensitizers; the patient is obliged to eat them if he would lose his distress rapidly.

It is important to remember that gastrointestinal food allergy differs considerably from inhalatory allergy in that the allergic food easily can be eliminated from the diet and yet the patient's daily food requirements readily can be satisfied. Hence "desensitization" is of very little importance in this disease.

However, in order to "hypo-sensitize" the patient to a particular food, one begins to feed him on small quantities of that food and increase it very slowly until the maximum tolerance is reached or until the patient can tolerate a reasonable quantity.

### DIET

(a) Remove the allergic irritant by withholding the following foods:

#### *Allergic Foods*

Tea, coffee, chocolate, soup (all kinds), syrup, liqueurs, sauces, gravies, beef juice, sour milk, sour cream, malted milk, prune juice, chopped meat, anything fried, anything stewed, spices, onions, radishes, horseradish, sugar, candy, cake, ice cream, pie, pudding, jelly, zweiback, toast, rye bread, bran, oatmeal, corn, wholewheat, mushrooms, cheese, sweet potatoes, herring, catchup, pepper, beans (dried or baked), apples (raw or baked), oranges, grapes, grapefruit, strawberries, figs, dates, raisins, corn flakes, condiments, stomachics, appetizers, pimento.

Patients suffering from food allergy of the digestive system are sensitive to the above foods. None of

these foods is allowed. Other procedures not allowed are: Heat to abdomen, laxatives and enemas.

(b) Feed the patient on the following foods:

#### *Anallergic Foods*

Eggs, soft or hard boiled; fish, boiled or broiled; chicken, boiled or broiled; beef, boiled or broiled; veal, boiled or broiled; lamb, boiled or broiled; liver, boiled or broiled; oysters, raw; sweet cream; butter; chicken fat; white bread, fresh or old; farina, with butter or cream; rice, with butter or cream; noodles, with butter or cream; macaroni, with butter or cream; cream of wheat, with butter or cream; custard; lettuce; tomatoes; potatoes, boiled, baked or mashed; green peas, boiled or steamed; string beans, boiled or steamed; cauliflower, boiled or steamed; brussel sprouts, boiled or steamed; spinach, boiled or steamed; carrots, boiled or steamed; seltzer, water; mayonnaise; salt; \*milk (limited), boiled; \*prunes (without the juice); \*pears, raw; \*bananas, raw; \*plums, raw; \*peaches, raw; \*cherries, raw; \*cantaloup, raw; \*honeydew melon, raw; \*cocoa (prepared).

Patients suffering from food allergy distinctly of the digestive system are rarely sensitive to the above foods. These foods also serve as hypo-sensitizers.

### CITATION OF ALIMENTALLERGY CASES

It was in 1922, when we began to follow the clue of alimentary food allergy. By 1925, we had fairly definite evidence of its existence, definite methods of treatment and the nature of results. Up to date we have treated nearly one thousand cases of alimentallergy, approximately half of them being ambulant, office patients. We cite several cases and call attention to certain special features.

*Case 1. Irritable Alimentallergy.* J. L. 27 years of age, female, married, one child, menses regular, weighing 86½ lbs. and measuring 5' 5", consulted us June 4, 1929.

*History and Complaints.* The patient had been vomiting for eight years, with remissions. She had been suffering also from nervousness, headache, nausea, heartburn, sour regurgitation, pressure in the epigastrium and a clogged feeling in her throat. During these eight years she gave birth to one child. The pregnancy of another had to be terminated on account of the extreme vomiting which became milder only, but did not cease after the termination of the pregnancy. She had consulted many physicians, went to many clinics and had been at one of the large hospitals in New York City for three weeks. There, many tests of her blood, spinal fluid, stomach contents and feces were made and gastrointestinal X-rays were taken, all of which proved to be negative. She vomited while at the hospital and continued to do so after being discharged from there and referred to the clinic. The patient came to us one year after she left the hospital.

*Examination.* The patient was a thin, pale individual with an anxious expression. Her heart and lungs were negative. The abdomen was scaphoid and tender in both iliac regions, otherwise negative. The nasal mucosa was red and the tonsils were large and spongy. The uterus was retroverted and the cervix lacerated. Rectal examination was negative.

*Diagnosis.* From the long duration of her complaints and from the negative findings at the hospital and at our office, we concluded that the patient was suffering from irritable alimentallergy.

*Treatment.* We instructed her to select her meals from the "anallergic foods" and especially to avoid the "allergic foods". We also gave her some medication but eliminated

\*Not allowed in the beginning or at any time should the symptoms recur, especially if bowels show tendency to move more than once daily.



it soon because she vomited immediately after taking it.

**Result.** All her symptoms including the vomiting disappeared in a few days. Her tonsils were removed on June 24, 1929. She continued to feel well on the diet and gained weight up to 104 pounds. After adhering a year to the "anallergic foods" she began to take small amounts of "allergic foods" occasionally. By the end of another six months she ate everything. Nevertheless, she was perfectly comfortable for another eight months.

**Recurrence.** On August 8, 1932, she began with nausea, heartburn, eructation and vomiting. She took cathartics and enemas for a week and became worse. On August 15, 1932, she presented herself at the office with these last named complaints. Examination proved her to be suffering from the same condition as at her first visit to the office, irritable alimentallergy. We advised her to return to the "anallergic foods", which advice, according to the subsequent statement of her husband, she did not follow. We did not hear from her for over a month when on September 29, 1932, we were called to her home. There, her husband informed us that she had insisted upon trying another physician who radiographed her alimentary tract, examined her blood and gastric contents and found them negative. He treated her for about a month without any improvement. By this time, the suffering from the gastrointestinal tract was so severe that she attempted to commit suicide by inhaling illuminating gas. After an ambulance physician revived her with the aid of a pulmotor, she asked her husband to call us.

During this visit her complaints were of the same nature but more pronounced. Examination revealed that she was suffering from irritable alimentallergy, as on several previous occasions. We advised her to resume the "anallergic foods", and were fortunate this time, because the nurse who was in attendance carried out our instructions faithfully. We also recommended an ice bag to the abdomen. The symptoms disappeared in a few days. She is well at this date.

**Comment.** It should be noticed, that the patient's complaints were confined to that part of the alimentary tract which extends from the mouth to the duodenum and were accompanied by general symptoms. She had no symptoms referable to the intestinal tract during the entire period of observation. Before she consulted us she had resorted to cathartics and enemas with the hope of relieving her gastric distress and her general symptoms. However, enemas or cathartics with frequent bowel evacuations had not cleared up her complaints. When the irritants were removed by excluding the "allergic foods," it mattered little whether she moved her bowels once a day or once a week, she remained comfortable in either event. The frequency of the bowel movements then depended upon the amount of food ingested. Little eating caused less frequent bowel movements, and the ingestion of much food caused more frequent or larger stools. This case is an example of *irritable gastrallergy*.

**Case II. Irritable Alimentallergy.** E. F., 26 years of age, female, married, two children, menses regular, weighing 135 pounds and measuring 5 feet 4 inches, consulted us February 18, 1928.

**History and Complaints.** The patient stated that she was suffering from constipation. On further interrogation it developed that she had one or two bowel movements daily. However, since she had a continuous desire to move her bowels she concluded that her bowel evacuations were incomplete. This condition she termed constipation. She used many cathartics without relief. She had consulted many physicians and they concurred in this opinion. They prescribed cathartics and enemas but the distress continued.

**Examination.** The physical examination including a rectal was negative. The urine was negative.

**Diagnosis.** Irritable alimentallergy. Since all symptoms were confined to the intestines the more specific diagnosis was *irritable enterallergy*.

**Treatment.** "Anallergic foods."

**Result.** Well up to date.

**Case III. Irritable Alimentallergy.** F. K., 28 years of age, single, school teacher, menses regular, weighing 95 pounds and measuring 5 feet, consulted us Jan. 7, 1925.

**History and Complaint.** Began many weeks ago, with several loose bowel movements daily, besides one solid evacuation. In addition to this she complained of gas in the stomach, distension of the abdomen and slight cramps at the time of moving the bowels. She also suffered from nervousness and occasional palpitation.

**Examination.** Patient appeared thin, pale and anxious. Blood pressure 120/80. Pulse 90. Urine negative. Basal metabolism: plus two. Stool contained blood but was negative to ova or parasites. Hemoglobin 65%. Nose and throat revealed an atrophic mucosa. Heart, lungs and extremities negative. The abdomen revealed fullness in the right side especially in the right iliac region, otherwise negative. Rectal examination negative. Gastrointestinal X-rays proved negative.

**Diagnosis.** Irritable alimentallergy.

**Treatment.** "Anallergic foods." Bismuth. Ice bag to the abdomen.

**Result.** The patient became well within a week.

**Progress.** The patient usually adhered to the "anallergic diet" during the attack and for a while after, but transgressed later. The result was that she had several attacks of diarrhea since then. In March, 1932, she had an attack of diarrhea accompanied by furuncles and arthritis. The diarrhea was controlled soon with the diet but the other symptoms continued. However, they cleared up after several hypodermic injections of a bacteriophage filtrate and a vaccine prepared from the patient's stool. Since then, the patient has adhered more strictly to the "anallergic foods" and remained free from gastrointestinal disturbances. This case is an example of *irritable colonallergy*.

**Case IV. Irritable Alimentallergy.** P. K., 34 years of age, male, married, weighing 185 pounds, and measuring 5 feet 8 inches, consulted us March 5, 1931.

**History and complaint.** The patient's most important complaint was that he could not move his bowels without a cathartic or an enema for many years. He also suffered from abdominal distension and borborygmi.

**Examination.** The physical examination was negative. Rectal examination revealed a large fecal mass.

**Diagnosis.** Irritable alimentallergy, more specifically irritable rectallergy.

**Treatment.** "Anallergic foods."

**Results.** The abdominal distension and the borborygmi cleared up in a few days. The only complaint the patient had for a while, was that when he attempted to move his bowels the fecal mass was too large to be evacuated conveniently. We instructed him to place the tips of his fingers on the perineum, a few inches to one side of the anus, and press to the opposite side and upward. This procedure thinned and cut the mass and facilitated its evacuation. This case is an example of *irritable rectallergy*.

**Case V. Autolytic Alimentallergy.** J. K., 44 years of age, male, married, weighing 133 pounds, and measuring 5 feet 3 inches, consulted us May 27, 1929.

**History and Complaints.** Eighteen years ago, the patient had typhoid fever. The only complication he could recall was blood in the urine (?) for two days. He recovered completely. Fourteen years ago, a pain began in the abdomen which continued for two years. His appendix was then removed and he felt well for four years. Eight years ago, the pain returned to the abdomen and in spite of all the treatment, the pain persisted up to the day he consulted us, with occasional remissions. He slept well and had one bowel movement daily.

*Examination.* General appearances was fair. Blood pressure 120 80. Pulse 60. Heart, lungs, abdomen, extremities, reflexes, nose and throat were negative. X-ray revealed a duodenal ulcer.

*Diagnosis.* Autolytic alimentallergy, more specifically autolytic duodenallergy.

*Treatment.* "Anallergic foods."

*Results.* The patient has been continuously well since he has been adhering to this diet. He gained fourteen pounds up to date. In June, 1930, gastrointestinal X-rays proved to be negative. This case is an example of *autolytic duodenallergy*.

The same striking results are seen in *infants and children*.

*Case VI.* H. W., a seven year old child whose father is a pediatricist, has been under our observation since June 20, 1932.

*History and Complaints.* The child vomited daily for years. The vomiting was preceded by pallor and faintness. Many physicians had treated him without success.

*Examination.* Examination proved negative.

*Diagnosis.* Irritable alimentallergy, more specifically *irritable gastrallergy*.

*Treatment.* "Anallergic foods."

*Result.* No vomiting up to date.

*Case VII.* S. F., a four and a half year old child whose father is a physician has been under our observation since July 10, 1932.

*History and Complaints.* The child vomited daily from birth and each vomiting was preceded by pallor and faintness. Many pediatricists had treated him without any beneficial effect.

*Examination.* The boy was thin and had a pale yellow complexion. Heart, lungs, abdomen, extremities, reflexes, nose and throat were negative.

*Diagnosis.* Irritable alimentallergy, more specifically *irritable gastrallergy*.

*Treatment.* "Anallergic foods."

*Result.* No vomiting up to date. The child gained weight, has good color and eats without difficulty.

### GENERAL COMMENT

At the present there is considerable confusion in the literature of this subject; many authors bewail this fact, as is evidenced by the following:

Crohn (5) states that the terms indigestion, dyspepsia, gastritis, neurosis, hypersecretion, and achylia form indistinct concepts in our minds, the one overlapping and being confused with the other, and therefore not clearly comprehended. For the most part, it would take a jurist of note, or an experienced logician to decide, among a group of medical men, just what was meant by many terms used in gastrointestinal ailments. What one would term "hyperacidity," another might call a "hyperacid gastritis"; what is a "functional anacidity" to one, is a "gastric neurosis" to the other.

Matthes (6) remarks that every physician is familiar with the complaints of a "weak" stomach and intestines. There are individuals with very sensitive stomachs, who are subject to pyrosis which continues

irrespective of the quantity or the quality of food; they regurgitate sour fluid at times to such degree that it even irritates the gums; there is a demonstrable hypersecretion and hyperacidity of gastric contents and, with it, spastic constipation. At other times, constipation alternates with diarrhea. Such conditions are chronic. They often start in childhood, and it would seem that constitutional factors play an important role. The patients are not always neuropaths in the sense of neurasthenia, but they do have digestive organs more sensitive than do average people. The most characteristic feature is the constitutional element; perhaps it is more appropriate really to regard it as a constitutional anomaly.

Bassler (7) states that it is most probable that it will always remain impossible in the living subject to diagnose just what is the detailed picture of the stomach layers in a chronic gastritis. Gastric analysis, state of motility, length of history, and subjective symptoms are all we have to work upon, and, with these, in our present state of knowledge, and unless we accidentally gain particles of gastric mucosa for examination, much of the diagnosis in the ordinary run of cases remains as a supposition, and thus the most logical basis of treatment remains fixed upon rather symptomatic standards.

In discussing the treatment of "alimentallergy," all authors advise the patients "to take it easy, eat slowly, and eat the proper food," about which food each one has a different idea. In the beginning, it is usually advised to eat "delicate" foods, but a few days later when the patient complains of constipation, roughage again is added. All physicians advise laxatives, some with vigor, and some with caution.

We may read one chapter on gastroenterology after another, and one analytical author after another, and always we find the same confusion and the same despair.

### CONCLUSION

The purposes of this paper have been:

- (1) To demonstrate the possible etiology of about fifty gastrointestinal "diseases" described as separate entities without known causes, in all standard text books.
- (2) To induce proof that all these fifty, separately described "diseases" really may be regarded only as different groups of symptoms of one disease viz "alimentallergy."
- (3) To detail a method of preventing and neutralizing the distressing effects of this disorder of nutrition.
- (4) To call attention to a method which obviates the customary routine of testing each patient for each allergic food.
- (5) To submit a method of eliminating cathartics and enemas in the treatment of "alimentallergy," a condition from which it is believed that the great majority of those who need cathartics to produce bowel evacuations suffer.

5. Crohn, Burril B.: Affections of the Stomach. W. B. Saunders Co., 1927, p. 283.

6. Matthes, M.: Differential Diagnosis of Internal Medicine, translated by I. W. Held and M. H. Gross, Blakiston's Son & Co. 1925, pp. 610-611.

7. Bassler, Anthony: Diseases of the Stomach and Upper Alimentary Tract. F. A. Davis Co., Philadelphia, 1926, p. 547.

## SECTION IV—*Roentgenology*

### Diverticular Sarcoma of the Stomach\*

By

JAMES T. CASE, M.D., D.M.R.E., F.A.C.S.  
CHICAGO, ILLINOIS

IT is very difficult to make a differential diagnosis between sarcoma and carcinoma of the stomach, as both the clinical and the roentgen findings are very much alike in the two forms of tumor. The age, the course, the results of palpation and the findings on examination of the stomach contents practically are the same in sarcoma as in carcinoma except that perhaps lack of free hydrochloric acid is rarer in the former than in the latter. Hemorrhage is seen in only about a third of the cases of sarcoma but when it occurs it is usually copious. Naegli (1) says that in some cases of sarcoma there is enlargement of the spleen and that, as this does not occur in carcinoma, it is a point in differential diagnosis. Metastases may occur at a greater distance and form larger masses than in carcinoma. There may be skin metastases which afford an opportunity for decisive microscopic examination of a biopsy specimen.

I have encountered two cases of sarcoma of the stomach in which I have had an opportunity to make a tissue diagnosis. One was a case of generalized gastro-intestinal lymphosarcoma in which the X-ray appearances were characteristic enough to form a basis for a correct diagnosis; the other case (presented here), was one in which a sarcoma developed in a diverticulum of the stomach wall.

A number of very elaborate papers have been published on sarcoma of the stomach, among which may be mentioned those in English by Haggard (2) and Douglas (3), (1920), by Balfour (4), (1930) and by D'Aunoy and Zoeller (1930). Haggard reviewed the subject up to 1920 and found that 244 cases had been reported in the literature, in 107 of which operation had been performed. Balfour recorded 54 cases from the Mayo Clinic. Masson (6) had previously reported 13 proved cases of gastric sarcoma from the Mayo Clinic including the cases up to 1920. Balfour found that between 1920 and 1930 the number had increased from 13 to 54. The diagnosis was made on operation in all but one, that one having been found on necropsy. In 5 cases no tissue was removed on operation, the surgeons having sufficient confidence in the gross appearance of sarcoma of the stomach to make the diagnosis from the macroscopic evidence. In three cases the pathologist was not quite sure, reporting "possibly sarcoma." D'Aunoy and Zoeller (5) report four personal cases and list the recorded cases in the literature

up to 1930, apparently without knowledge of Balfour's paper, bringing the number up to 335.

My limited experience with this rare lesion does not justify any dissertation on the general subject of sarcoma of the stomach, but the peculiar features of my second case in which the sarcoma was associated with a diverticulum warrant a detailed report of the case and some discussion. Myomatous tumors have often been observed to develop malignant properties after varying periods of benign growth. Schiller (7), Kimpton (8), Warner (9) and others report cases in which a tumor existed for a long period without causing symptoms but was finally removed because signs of malignancy developed; the microscopic diagnosis was sarcoma. Warner declares that a leiomyoma of the stomach may undergo sarcomatous degeneration just as may a leiomyoma of the uterus. Bachrach (10) believed that leiomyomata of the stomach may become malignant. Bullock (11), Haggard (2) and Fenwick (12) shared this opinion. Gosset, Bartrand and Loewy (13), however, maintain that many of the pediculated so-called "sarcomata" of the stomach are and remain benign.

There has been a further discussion as to whether in leiomyosarcomata of the stomach the smooth muscle cells have become transformed directly into sarcoma cells or whether the myoma has been invaded secondarily by a sarcoma originating from the connective tissue of the stroma. In the cases of Brodowski (14) and Virchow (15) direct sarcomatous degeneration of a leiomyoma of the stomach wall is described, and in the case of Gouilloud and Mollard (16) the pathologist who made the histological examination concluded that it was a tumor developed from smooth muscle tissue. Lecène and Petit (17), however, consider it much more probable that the connective tissue stroma of a myoma has undergone sarcomatous degeneration.

As both sarcoma and diverticulum of the stomach are unusual it is extremely rare to find the association of the two lesions in the same patient. Benign growths have been reported in diverticula of the stomach. Sandström (18) in 1929 reported a case of this rare lesion, interesting from the point of view of differential diagnosis, in which roentgen examination of the stomach showed narrowing of the lumen of the pylorus which had the appearance of a defect, in the center of which there was a niche-like opaque spot. A tentative diagnosis of ulceration surrounded by infiltration was made from the roentgen findings. On operation the surgeon found a benign tumor-like hyperplasia of the

\*Professor and head of the Department of Radiology, Northwestern University Medical School, Chicago.  
Submitted February 9, 1935.



Fig. 1. Photograph of diverticular myoma of the stomach reported by Puskepellies; cited by Sandström.

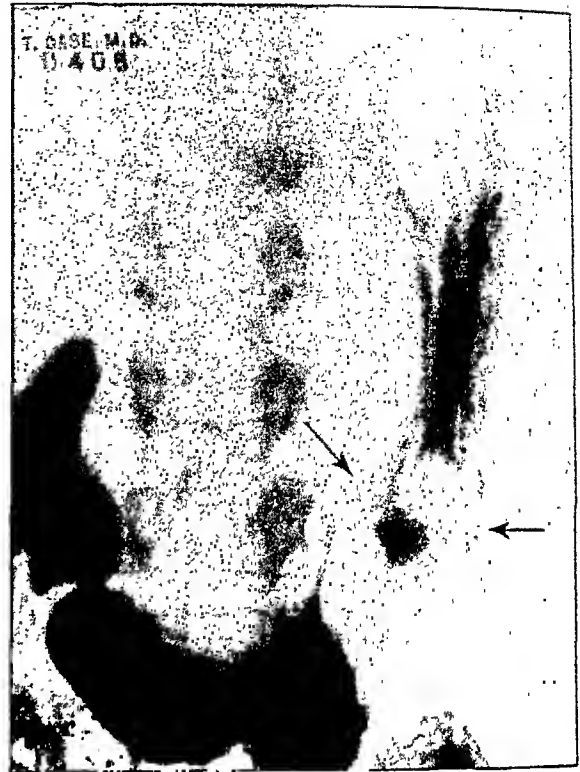


Fig. 2. Diverticular ulcerating sarcoma of the stomach. Patient prone. Filling defect in the stomach and near the center of defect a niche containing the ulcer crater.



Fig. 3. Patient erect. Filling defect simulating "pad" sign of a malignant ulcer. At operation this proved to be a residue of barium in a diverticulum.

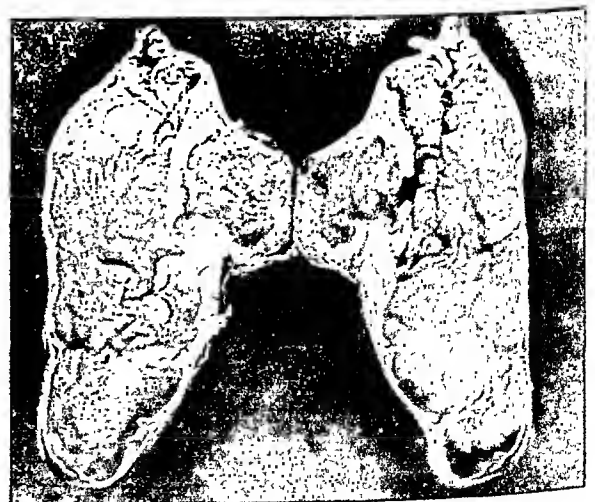


Fig. 4. Photograph of removed portion of stomach (sectioned) containing the diverticulum.



Fig. 5

Fig. 5. Low power (23 x) photomicrograph of section of diverticular sarcoma of stomach.

was congenital and that the degeneration took place later in life. He refers to three cases of myoma described by Puskeppelies (20) in which that author expressed the opinion that the myomata were primary and the diverticula had formed in the tumor tissue. Cleve rejects this interpretation and thinks the diverticula were primary. He believes his tumor was sarcoma though there were no metastases and no infiltrating growth. The predominant cells of the tumor showed a decided similarity to smooth muscle cells, particularly in the form of the nucleus; they also resembled the cells of spindle-cell sarcoma. He assumes that the tumor cells had originated from connective tissue cells and in the process of further differentiation had stopped at the stage of smooth muscle cells.

Müller (21) describes a carcinoma diverticulum of the stomach.

In the light of these reported cases of diverticular tumor and the interesting fact that, in my own case which will now be reported, there was a tumor in the wall of a diverticulum diagnosed on microscopic examination as sarcoma, the question arises whether there was not primarily a leiomyoma of the stomach which later became malignant.

#### CASE REPORT

Mr. C. L. E., age 52, reported for examination and treatment on February 24, 1930. He complained of biliousness and dizziness and headaches with anorexia dating back about a year. I found that he had had the usual diseases of childhood, including typhoid when about 14. Thirteen years ago he went to New Mexico on account of pulmonary tuberculosis; the present examination showed healed tuberculous lesions of the lungs. In New Mexico he increased from 115 to 143 pounds in weight, which he maintained until recently when he began to suffer digestive disturbances. His weight had fallen to 110 pounds,

pyloric glands in the submucosa and muscularis, surrounding a central diverticulum, from which he made a diagnosis of diverticular adenoma, or more correctly perhaps, an adenomatosis combined with a diverticulum.

Such benign diverticular tumors (diverticular myomata or adenomata) are very rare and Sandström was able to find only one case reported in the earlier literature in which roentgen examination had been made. In that case also the roentgen findings were wrongly interpreted. Because of the joint presence of a diverticulum and a tumor in these cases diagnosis based on the roentgen ray findings alone is extremely difficult. A niche-like opaque spot surrounded by a defect in the gastric shadow has been recognized as a characteristic feature of malignant ulcer, though it has been found in some of the larger calloused ulcers also. It is almost impossible, therefore, to exclude ulcer in cases in which ulcer or cancer is suspected on clinical grounds. To make a correct roentgen diagnosis these cases might be followed up with repeated examinations for some considerable time, preferably after an ulcer regime, after which the findings should remain stationary if it is a case of tumor; but valuable time would be lost in the waiting. In these cases absence of spasm is a point against ulcer. The absence of blood in the stools is also an important point in the differential diagnosis from ulcer.

One of Balfour's cases was a sarcoma in a diverticulum and Cleve (19) reports a case. Though his title is "diverticular myoma of the stomach," he concludes from the histological examination that the tumor was a sarcoma. The patient was a man of 61. Necropsy showed a diverticulum of the stomach which had been transformed entirely into a tumor that had undergone sarcomatous degeneration. He thinks the diverticulum

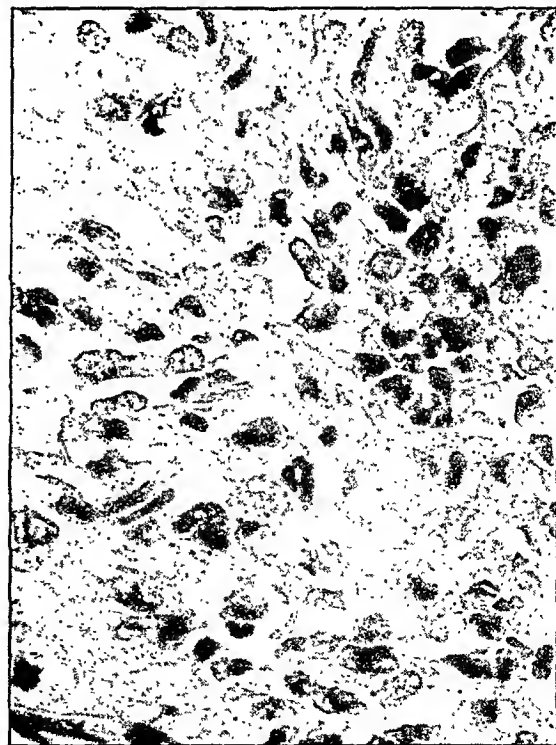


Fig. 6

Fig. 6. High power (550 x) photomicrograph from resected tumor.



but under the care of Dr. Mendelson he had regained 14 pounds.

Our examinations showed old scars of tuberculosis in the apices of the lungs and marked enlargement of the spleen with calcifications. The roentgenogram of the stomach showed a crater at about the middle of the body of the stomach, about one-half inch in diameter, surrounded by a filling defect which we believed represented a tumor. The remainder of the gastro-intestinal examination was without importance. The blood count showed 4,750,000 red cells and 11,500 whites. The urine findings were normal. Gastric analysis showed free hydrochloric acid as high as 45 at the end of an hour, and gross blood in the fasting stomach contents. The pre-operative diagnosis was an "ulcerating lesion in the middle of the body of the stomach, rather near the greater curvature, with tumor formation."

On operation, I found such a large tumefaction around the apparent ulcer that I felt that the lesion must be malignant. There was a mass measuring 4.5 cm. in diameter along the base located on the anterior wall of the stomach near the greater curvature and extending 2.5 cm. from the outer surface of the stomach. The tumor was resected together with the distal portion of the stomach by the method of Polya, making the gastrojejunal anastomosis retrocolic. The liver was normal.

The specimen showed a diverticular formation, the crater being an inch deep and apparently having an ulcer at its

base. It is interesting to note that there were no adhesions to the diverticular mass except a few omental tags, so that a traction diverticulum hardly could be considered.

On gross examination the mucosa was found to be smooth and free from change except for a sharply punched-out opening which communicated with the hollowed out interior of the mass seen externally. This interior surface was ulcerated, rough and irregular, covered by fibrin. The wall was firm, pinkish-white in color, with numerous hemorrhagic areas.

Microscopic study by Dr. H. R. Fishback follows:

Sections cut from the localized out-pouching of the stomach wall show microscopically ulceration with entire loss of mucosa, the ulcer base being covered with fibrin, beneath which is granulation tissue mingled with tumor cells. Tumor cells comprise a mass making up almost the entire thickness of the wall with infiltration and destruction of the mucosa, submucosa and muscularis. The cells are arranged closely together with a small amount of fine reticulum. They are of various sizes and shapes, mostly of rounded or cuboidal form. The nuclei are large, tend to hyperchromatism and are of loose reticulated structure. Mitotic figures are not seen. Many blood spaces are found lined by tumor cells.

Diagnosis: Mixed cell sarcoma of the stomach.

The patient at last report, nearly three years after operation, weighed about 135 pounds and was able to carry on his usual occupation of store manager.

## REFERENCES

1. Nagels, Th.: Die klinische Diagnose der Bauchgeschwülste. München, J. F. Bergmann, 1926, p. 273.
2. Ingegard, William D.: Sarcoma of the Stomach. With report of a case and 107 cases operated upon. *S., G. and O.*, 1920, xxxi, 505.
3. Douglas, John: Sarcoma of the Stomach. With report of three cases. *Ann. of Surg.*, 1920, lxxi, 628.
4. Balfour, Donald C., and McCann, James C.: Sarcoma of the Stomach. *S., G. and O.*, 50:948, June, 1930.
5. D'Aunoy, Rigney and Zoeller, Adelaide: Sarcoma of the Stomach. Report of four cases and review of the literature. *Amer. J. Surg.*, 1931, n.s., lx, 443.
6. Mason, James C.: Quoted by Balfour, Reference No. 4. above.
7. Schiller, Max: Ueber einen klinisch und histologisch eigentümlichen Fall von primärem Magen-sarkom. (In case of primary sarcoma of the stomach peculiar clinically and histologically). *Arch. f. Verdauungskr.*, 1914, xx, 179.
8. Kimpton, A. R.: Primary Sarcoma of the Stomach. Review of the case six years after operation. *Boston M. and S. J.*, 1919, clxxxi, 731.
9. Wyrner, E.: Sarcoma of the Stomach. *Ohio M. J.*, 1917, xiii, 647.
10. Incebrach Robert: Myoma sarcomatodes des Magens. (Myoma sarcomatodes of the stomach). *Med. Klin.*, 1916, xii, 825.
11. Bullock, Howard and Shearman, C. H.: A case of sarcoma of the stomach. *Med. J. Australia*, 1928, ii, 651.
12. Fenwick, Samule and Fenwick, W. Soltau: Cancer and other tumors of the stomach. Phila., P. Blunkiston's Son & Co., 1903.
13. Gosset, A.; Bertrand, Inn., and Loewy: Tumeurs pediculées de l'estomac dites "sarcomes." Pediculated tumors of the stomach called sarcomata. *J. de chir.*, 1924, xviii, 677.
14. Brodowski, W.: Ein ungeheures Myosarcom des Magens nebst sekundärem Myosarcomen der Leber. An enormous myosarcoma of the stomach with secondary myosarcomas of the liver. *Virchow's Arch. f. path. anat.*, 1876, lxxvii, 227.
15. Virchow, Rudolph: Die krankhafte Geschwülste. Pathological tumors. 1865, iii, 130.
16. Goulloud, P., and Mollard, J.: Cancer musculaire de l'épiploon et de l'estomac. Myomatous cancer of the omentum and of the stomach. *Lyon med.*, 1889, lxi, 545.
17. Lucene, P., and Petit, J.: Le sarcome primitif de l'estomac. *Rev. de gynec. et de chir. abd.*, 1904, viii, 965.
18. Sandstrom Carl: Contribution to the roentgenological appearance in cases of benign diverticular growths of the stomach. *Acta radiol.*, 1923, x, 427.
19. Cleve, A.: Divertikel und Divertikelmyome des Magens. (Diverticulum and diverticulum myoma of the stomach). *Virchow's Arch. f. path. anat.*, 1925, cclv, 373.
20. Puskepellies, Max: Über divertikuläre Myome des Magen-Darmtractus mit Hinweis auf die Malignität des Myome. (Diverticular myomata of the gastro-intestinal tract and discussion of the malignancy of myomata). *Virchow's Arch. f. path. anat.*, 1925, cclv, 373.
21. Müller, Emil: Ein Fall von Karzinomdivertikel des Magens. (A case of carcinoma diverticulum of the stomach). *Munch. med. Wchnst.*, 1919, lxxvi, 513.

## ABSTRACTS

PFALLER, G. E.

*The Roentgenological Diagnosis of Meckel's Diverticulum. S., G. and O., Vol. LIX, No. 6, Dec., 1934, pp. 929-935.*

Meckel's diverticulum has been defined as a diverticulum of the small intestine varying in its length, the diameter of its lumen, and in its position on the terminal part of the ileum. It exists in about two per cent of all individuals, and is commonly found at autopsy.

When inflamed it gives rise to symptoms which resemble those of acute appendicitis. Fibrosis at its base may cause intestinal obstruction. Intussusception may occur at the site of the diverticulum. Perforation of a peptic ulcer of Meckel's diverticulum produces signs of acute intestinal perforation. The most frequent symptom, however, is

haemorrhage from the bowel. When this occurs in a child, one should think first of a Meckel's diverticulum.

In the author's experience repeated examinations of the small intestine may be necessary to show the diverticulum. In making such examinations one should keep in mind that the diverticulum may be located at any point on the circumference of the bowel. The diverticulum may be filled with a non opaque substance preventing the entrance of barium. The characteristics of the diverticulum are the same as those of any diverticulum; it is apt to show peristalsis. The author reports 2 cases in which the diagnosis of Meckel's diverticulum was made roentgenologically, and found at operation.

Six figures accompany the article.

N. M. Percy, Chicago.



## SECTION V—*Therapeutics*

### The Use of Duodenal Extract as an Adjuvant in the Treatment of Benign Peptic Lesions: Report of Eight Cases\*

By

ANDREW B. RIVERS, M.D.  
ROCHESTER, MINNESOTA

IN October, 1934 (11), I suggested that some beneficial results might accrue from the use of an extract of duodenal mucosa and submucosa as a supplement to approved methods of treating benign peptic lesions. Thus far more than fifty patients have been treated in this way, many of them with encouraging results. In this paper are reviewed the results in a few of the cases in which this treatment was used. That this method of treatment in no way reduced the effectiveness of other methods of therapy, indeed that the usefulness of other methods may have been augmented by such a procedure, is suggested by the clinical as well as by the roentgenologic results obtained in these cases. It should be stated here that no form of treatment which considers solely the early symptomatic results, even though these be most encouraging, can merit serious consideration unless such results give some promise of enduring benefit.

It is well known that many types of treatment instituted for the relief of the symptoms of peptic ulcer may be very effective in controlling the distress associated with this disease. The medical literature and physicians' correspondence are deluged by well-sponsored new treatments for ulcer, which are welcomed and tried with enthusiasm only to be discarded and forgotten with equal promptness. These treatments last just long enough for the normal cycle of re-appearing difficulties to return, and on the re-institution of symptoms each system in turn loses cast, and there is a return to the old approved methods of treatment.

The cases reported in this paper have not been observed sufficiently long to permit drawing any definite conclusions regarding the usefulness of duodenal extract in the treatment of ulcer. I am encouraged in continuing to use it, however, because not only were these patients relieved of their symptoms, but in all cases included in this particular report there was roentgenologic evidence of ulcers having healed.

#### A CONSIDERATION OF SOME OF THE CAUSES OF ULCER AND A RATIONALE FOR THE USE OF DUODENAL EXTRACT

Treatment of any disease should include some plan whereby factors of known etiologic importance can be recognized and some effort made to subjugate or ameliorate them. Although there are many interrelated factors which are important in the causation of ulcer, these ultimately resolve themselves around two, the

one inherent in the ulcerating potentiality of acid-pepsin, the other maintained in the defense which the tissues possess and by which they protect themselves against the eroding action of the gastric chyme. It would seem that the alternating activity and quiescence which are so characteristic of such lesions would be evidence of two forces, the one of aggression and the other of defense, and that the outcome would depend on which factor was dominant at any particular stage of the life cycle of peptic ulcer.

Physiologists have amply demonstrated the increased vulnerability of tissues to the eroding action of gastric juice which has greatly accentuated acid-pepsin values. The factors of aggression inherent in acid-pepsin, however, are ordinarily insufficient to produce ulceration in tissues which maintain their normal mechanisms of defense.

*Defense mechanisms of duodenal mucosa.*—Mann and Kawamura made some inquiries into the protecting, defensive mechanism of duodenal mucosa. They completely removed the duodenum of experimental animals; a loop of jejunum was then placed where previously the duodenum had been, thus reestablishing the regular continuity of the gastro-intestinal tract. The bile and pancreatic juice were drained into the jejunum, thus retaining the normal, physiologic extraduodenal antacids. In 20 per cent of cases ulcers developed at the point where the jejunum was anastomosed to the stomach. This suggests that the duodenal mucous membrane includes a protecting mechanism that is not possessed by the jejunal mucosa. It is not fully understood whether this increased resistance is inherent in the duodenal cells, whether the cells produce a secretion that adheres to the mucosa and makes it less vulnerable, or whether a substance is elaborated in the wall of the duodenum that alters gastric chemism to curtail its eroding properties.

Baker, Florey and Harding were of the opinion that the normal secretion of Brunner's glands aids in protecting the mucosa from injury by the acid chyme. Florey and Harding intimated that the specific factor of protection may lie in the mucoid consistence and contained alkalies of the product of these glands. Kosaka, Lim, Ling and Lui, and lately, Ivy have suggested that intestinal mucosa contains a substance which is absorbed and causes inhibition of gastric secretions.

*Defense factors inherent in pancreatic juice and bile.*—Mann and Williamson further pointed out the

Submitted March 16, 1935.  
\*Division of Medicine, The Mayo Clinic.

protective importance of the secretions which are poured into the duodenum by glands that are extrinsic to the gastro-intestinal tract. They performed some experiments in which the bile and pancreatic juices were drained away from the duodenum into the ileum. In 50 per cent of such cases peptic ulcer developed. In these experiments normal gastroduodenal continuity was maintained, the gastric chyme impinging on the area intended by Nature to receive it; yet, the loss of pancreatic juice and bile was sufficient to disturb the balance between the aggression mechanism inherent in the chyme and the defense mechanism inherent in the duodenal tissue, at any rate sufficiently so that dissolution of the duodenal mucosa occurred in 50 per cent of such cases.

McRoberts showed that the *pH* of the duodenum is maintained toward the acid side for much longer periods following a fat meal when the bile has been diverted in such a manner that it does not reach the duodenum. Hoerner evulsed the pancreatic ducts, making it impossible for the pancreatic secretion to enter the duodenum; he found that under such conditions the acidity of the duodenum was greater and was maintained for much longer periods. It would appear, therefore, that the bile and pancreatic juice have an important rôle in protecting the duodenal mucosa against the eroding action of the acid chyme. Duodenal mucosa elaborates *secretin* and possibly other hormones which act upon the pancreatic and possibly the biliary output.

*Defense factors inherent in duodenal chemism and mucosa.*—Mann and Williamson also developed experimental procedures by which the gastric contents were led directly into the jejunum without receiving the admixture of bile, pancreatic, and duodenal secretions. They drained the duodenal content into the ileum. Furthermore, the possible protecting mechanism of the duodenal mucosa was eliminated by substituting the jejunum where normally the duodenum existed; thus the possibility of protection from duodenal mucosa, duodenal secretions, and from bile and pancreatic juice was not available and the jejunal membranes had to resist, as well as possible, the eroding action of the acid chyme. Following this procedure, jejunal ulcers developed in 95 per cent of cases.

*Breakdown of duodenal defenses against acid-pepsin erosion.*—Stevens, in studying the capacity of the duodenum to neutralize and buffer acid, demonstrated that this organ had a remarkable reserve function in this respect, which was materially in excess of its ordinary physiologic requirements. That it will break down, however, under the necessity of neutralizing without interruption the acid chyme is shown by the work of many physiologists. Mann and Bollman instilled 0.4 per cent hydrochloric acid into the stomachs of dogs at a rate of less than 1 c. c. each minute for about eight hours daily. These animals appeared to get along very well for several weeks, after which time peptic ulcers usually developed.

Baker, Florey, and Harding studied the effect of hydrochloric acid on the duodenal cells of animals which had been fed it. Baker sacrificed his animals at varying times after feeding them hydrochloric acid of 0.2 to 0.5 per cent concentration. The first response of the duodenal cells to the feeding of acid was to pour out copious amounts of secretion. This was also noted by Florey and Harding. Baker additionally found that, if he continued to feed acid, the duodenal epithel-

ium would promptly disintegrate. If this was continued, bleeding from the membrane usually would result. On the other hand, if the feeding of acid was stopped, a remarkably rapid regeneration was noticeable, and in forty-eight hours the epithelium was usually again normally intact.

Gastric secretory rates are usually accentuated among patients who have peptic ulcer. This is especially noticeable among patients with duodenal or jejunal ulcer, and particularly so during periods when there is definite ulcer activity.

For some time I have been interested not only in the height of the acid concentration and peptic activity, but also in the ability of the chief and parietal cells to maintain a vigorous secretory rate for unusually long periods. It has often been noted that, following the use of histamine, patients with peptic ulcer continued to secrete a highly concentrated acid for considerable periods after a drop in acidity would ordinarily have been expected. If such cellular behavior actually obtains in response to other stimuli, it would be obvious that the gastroduodenal defense mechanisms of patients with peptic ulcer might be forced to exert themselves accordingly. It would seem to me that this adequacy in defense is one of the crucial factors in the cause of ulcer and that it would therefore merit special consideration in the treatment of such lesions. It seems logical that the activity of the defense mechanisms would have to fluctuate in proportion to changes in the potency of the mechanisms of aggression: with prolonged and sustained elevation of acid-pepsin secretion would develop a correspondingly vigorous effort of the cells to throw out defenses against such accentuated tendencies to erosion. Ordinarily, the daily physiologic fluctuation in the curves of acidity shows alternate periods of rapidity and retardation of the secretory rate, thus giving the cells "breathing spells" during which the forces of defense could be adequately reestablished. Physiologists have shown that *continuous* feeding of hydrochloric acid is likely to cause the eventual break-down of the cells called upon to resist the digestive action of the gastric chyme. It seems reasonable to assume that an important cause of such cell dissolution, which results in peptic ulcer, lies in the exhaustion of the defensive powers of the cells: they may have used up their own as well as all available reserve sources of defense.

The curve above the line in the upper portion of Figure 1 indicates the height of hydrochloric acid concentration following the use of histamine in Case 1 in this paper; the curve below the line is an exact inversion, or a mirror reflection, of the same curve. It will be noted that the acids remain relatively high for a prolonged period. The curve above the line in the lower portion of Figure 1 indicates a hydrochloric acid concentration following the administration of histamine to a patient who did not have peptic ulcer; again, the curve below the line is an inversion of the upper curve. The return to basic levels is relatively rapid. This serves to illustrate the wide differences which might exist in the requirements for tissue defense. The mirrored or inverted curves are drawn to illustrate the hypothetical degree of "protective" activity required of cell defense mechanisms, assuming that the comparative degree of activity of cell defense parallels to some degree the height and persistence of chief and parietal cell activity.

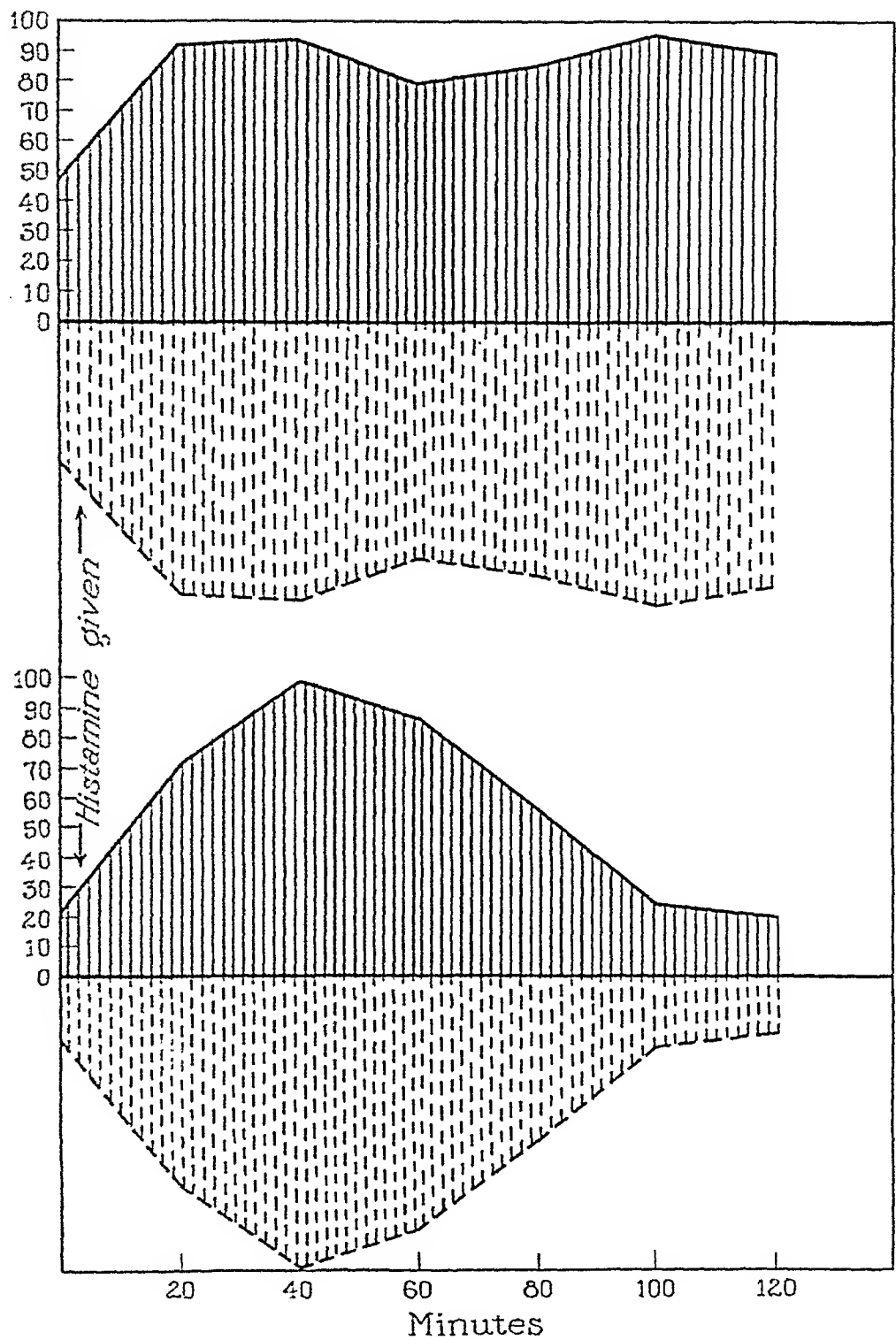


Fig. 1. Curves of free HCl concentration: UPPER, after administration of histamine to ulcer patient, Case 1; LOWER, after administration of histamine of a patient who did not have peptic ulcer.

In most instances present methods of treatment concern themselves mainly with the reduction or neutralization of gastric acidity. Admittedly, healing seems to be favored when this is accomplished; however, so soon as the acidity of the gastric chyme gets out of control, the threat of further erosion appears. Treatment of peptic ulcer would be more effective if somehow instead of diluting the acids and curtailing the peptic activity, the secretory rate of the chief and parietal cells could be subjugated or controlled at will. It seems that the defense mechanisms also need occupy the attention of those who are concerned with the problems of ulcer therapy. If total duodenal or gastric defense functions could be augmented, if specific substances could be made available so that we could control the duodenal secretions as well as the juices entering the duodenum, the problems of ulcer therapy would no doubt be greatly simplified.

In formulating a plan to support or reestablish tissue defenses, it would be well to take into consideration certain pertinent observations made by physiologists. The duodenal cells seem especially resistant to erosion by acid-pepsin. One of the first responses that occurs in animals when it might seem necessary for these cells to protect themselves is the throwing out of a copious amount of an alkaline secretion. This seems mainly to be a product of the glands of Brunner. Florey and Harding suggest that "malfunctioning of these glands may be primarily responsible for duodenal ulcer." At any rate, this secretion probably plays some rôle in protecting duodenal mucosa. It would seem, therefore, that if this secretion could be maintained or increased, or if the product of these glands could in some way be supplied to the duodenum, its protective powers might be restored or more consistently preserved.

The absence of bile and pancreatic juice definitely increases the vulnerability of the duodenal cells to erosion by acid chyme. Whether this is so because of the chemical reactions within the duodenum, or whether the availability of bile and pancreatic juice for gastric regurgitation constitutes the intimate mechanism of protection, seems of no great importance. The assurance that liberal amounts of bile and pancreatic juice are present in the duodenum might therefore be desirable in the treatment of ulcer. Secretin is elaborated in the duodenal mucosa, and perhaps other hormones as well and this affects the output of pancreatic juice and possibly bile. Some attention to ways of safeguarding the availability of these substances would also be useful in the treatment of ulcer. Furthermore, the evidence that the intestinal wall prepares a substance which is an inhibitor of gastric secretion is interesting and important. Treatment of peptic ulcer might be greatly improved by the use of such a substance. If by any means the work of the duodenal cells can be facilitated, if protective, alkaline duodenal secretions can be abundantly maintained, or if a product of the intestinal wall which lowers gastric acidity becomes available, progress in the treatment of peptic ulcer will be assured.

Prompted by the desire to make available certain substances which might be useful in the defense or rebuilding of besieged gastroduodenal tissues, an extract of duodenal mucosa and submucosa was prepared and supplied to patients who were suffering with peptic lesions. This extract was not intended to be used as a substitute for other therapeutic measures

but as a supplement to other methods of treatment.

In a previous paper I (10) pointed out that there must be several interacting factors responsible for the genesis and chronicity of peptic lesions. The most important of these factors were: (1) local traumatization of tissues, as by infected emboli, (2) acid-pepsin aggression and resistance of tissues to erosion, and (3) certain systemic factors, of which neurogenic influences seemed the most important. Since peptic ulcer is probably the result of interaction of several or all of these factors, it becomes necessary in formulating a plan of treatment to direct attention to all of them.

#### METHOD OF USING DUODENAL EXTRACT IN TREATMENT

The extract which has been used at this Clinic is obtained from the mucosa and submucosa of the duodenum of hogs.\* We are also using an extract made from the mucosa and submucosa of the pyloric portion of hogs' stomachs. At the present time Dr. Foley, Dr. Goldsmith and I are preparing a more detailed analysis of the early results noted from the use of these extracts in more than sixty cases. In all of the cases reported in this paper, the patients have been hospitalized and have been kept under careful observation. They were kept in bed for two or three days, following which they were permitted to be up three or four hours daily. During the first few days they were given a diet consisting almost exclusively of milk. Four ounces of milk were given every hour, beginning at 7 a. m. and continuing to about 9 p. m. In a few instances hourly feedings of milk were supplemented by the use of cereal, custard, and cream soup at meal times.

About the third day of treatment the intake of food was increased and patients were given small meals, consisting of soups, cereals, custards, puréed vegetables, and food of like consistency. Frequent feedings of milk throughout the day were continued. At 9:30 a. m., and at 2:30, 5:30 and 9:30 p. m., they were given 15 grains of alkali. At 10:30 a. m. and at 3:30 and 7:30 p. m., 30 grains of extract were given; this was usually mixed with 2 ounces of malted milk, egg-nogg, or grape juice. Sedatives and belladonna were used three or four times daily. Usually, after five or six days, the patients were given a bland type of diet, similar to that given to ambulant patients with ulcer. Milk was given once between meals and at 9 p. m. Twenty grains of alkali were then given an hour after meals, and 30 grains of duodenal extract were given at 11 a. m. and at 4:30 and 7:30 p. m. Throughout the period of hospitalization these patients were given mineral oil or olive oil several times daily.

The patients were then dismissed with the recommendation that they continue to take a bland, non-irritating diet and that they use 20 grains of alkali at 9 a. m., 4 p. m. and 7:30 p. m. Additionally, it was suggested that they take 30 grains of the extract, with a glass of milk, at 10:30 a. m., 3 p. m. and before retiring.

#### REPORT OF CASES

*Case 1.—Duodenitis type of duodenal ulcer.*—A man, aged twenty-four years, came to this Clinic complaining that for three years he had experienced reappearing episodes of epigastric distress. His symptoms reached their maximal intensity two hours after meals, and he was

\*Dr. Klein, of the Wilson Laboratories in Chicago, has kindly furnished us with this Extract.

usually relieved by the ingestion of food or soda. During the previous year there had been some intensification of his symptoms and he had noted less adequate relief by the use of soda. Physical examination was negative. Roentgenologic investigation revealed the presence of a "duodenitis type of duodenal ulcer". He was hospitalized in August, 1934, and placed on a Sippy regimen. Under histamine stimulation the gastric acidity rose to 124 for total acids and to 106 for free hydrochloric acid. The amount of pepsin was tremendously increased, rising on one occasion to 9000 units. The patient's diet was gradually increased and the regimen was supplemented by the use of 50 gm. of mucin daily. He was dismissed on an ambulatory regimen which consisted of a bland diet and 60 grains of alkali and 60 gm. of mucin daily. He was advised to curtail his activities and to obtain more rest. He improved temporarily, but after several months was again having trouble.

He returned and was again hospitalized. This time he was given a bland diet and 60 grains of alkali and 90 grains of duodenal extract daily; in addition he was given atropine and a barbiturate four times a day. He improved promptly and, after eight days, roentgenologic evidence of duodenal deformity had disappeared completely.

*Case 2.—Jejunitis following gastro-enterostomy.*—A man, aged fifty years, had at the age of forty-five undergone a posterior gastro-enterostomy and appendectomy for duodenal ulcer and appendicitis. He had been well for eighteen months following this operation, but during a period of much worry and tension he again had indigestion, which suggested recurring peptic ulcer. A roentgenogram was taken and gave evidence of a jejunal deformity that was assumed to be a jejunal ulcer. He was placed on a medical regimen and he improved promptly. Several months prior to his admission to this Clinic, he had again had indigestion and this had been complicated by the vomiting of blood. He had also noted tarry stools for a week. A month before admission he had had another hemorrhage.

On examination, there was evidence of secondary anemia. Roentgenologic examination showed a deformed duodenal cap; additionally, there was a definitely deformed region in the jejunum, which was assumed to be due to an "area of jejunitis". The patient was hospitalized and placed on a third-week Sippy diet. He was given 60 grains of alkali and 90 grains of duodenal extract daily. He was also given barbiturates and atropine twice daily. He promptly improved and, after eight days' hospitalization, another roentgenogram was taken. At that time the deformity of the jejunum had disappeared completely.

*Case 3.—Duodenal ulcer with a large crater.*—A man aged sixty, stated that for the past three years he had had indigestion, which frequently had been intensified during the spring and autumn. These episodes had lasted for a variable length of time, usually for two or three weeks. The pain was midepigastria in situation and occasionally was projected toward the right costal margin. The distress reached its maximal intensity from one to two hours after the ingestion of food and was relieved by soda or milk. The patient had noted tarry stools on one occasion. There was some evidence of dental infection but physical examination otherwise revealed nothing of importance. A roentgenogram of the gastro-intestinal tract disclosed a duodenal ulcer with a large crater. Estimation of the gastric acidity gave values of 100 for total acids and 90 for free hydrochloric acid. The amount expressed was not unusual. The infected teeth were removed, and the patient was hospitalized December 8, 1934. He was put on a bland diet, and was given 60 grains of alkali and 90 grains of duodenal extract daily. He was also given barbiturates and belladonna twice a day. His

symptoms promptly disappeared. On December 21, 1934, he was reexamined under the fluoroscope and at that time the crater in the duodenum had disappeared completely.

*Case 4.—Duodenal ulcer with a central crater.*—This patient, a man aged thirty-four, presented himself for investigation because of indigestion which had begun seven years ago. Four years prior to admission a diagnosis of peptic ulcer had been made, whereupon he had been placed on a Sippy regimen with prompt relief of symptoms. He had remained well for about a year, but had then manifested recurring difficulties by vomiting a copious amount of blood. Subsequently, he had had intervals of epigastric distress, varying in severity. During the last few months he had trouble with his stomach every day. This had been characterized by pain in the midepigastrium, which had come on from one to one and a half hours after meals and had been relieved by the ingestion of food or soda. Nothing unusual was demonstrated on physical examination. Estimation of gastric acidity, following the use of histamine, showed a maximum of 126 for total acids and of 110 for free hydrochloric acid. Roentgenologic investigation revealed the presence of a duodenal ulcer with a central crater. The patient was placed on a bland diet, and was given 60 grains of alkali and 60 grains of duodenal extract daily. Additionally, he was given a barbiturate and atropine three times daily.

After two weeks' hospitalization, a second roentgenologic examination of the gastro-intestinal tract was made; at that time, no duodenal ulcer crater could be visualized either under the fluoroscope or in the roentgenogram.

*Case 5.—Gastric and duodenal ulcers.*—A woman, aged thirty-six on admission to this Clinic, at the age of eighteen had had her appendix removed. Five years later she had undergone an operation for intestinal obstruction and two years after that, at the age of twenty-five her gall-bladder had been removed. All of these operations had been performed elsewhere. Following the cholecystectomy the patient had been well for two years. She had then, however, begun to have epigastric distress, which came on thirty minutes after meals and was relieved by the ingestion of soda. Three years before her admission to this Clinic she had been placed on an ambulatory ulcer regimen, with some relief of symptoms.

At the time of consultation at this Clinic the patient was having distress in the right hypochondrium, slightly to the right and slightly above the umbilicus; in addition, she experienced pain near the left costal margin. This was at times projected through to the lower left scapular region. These pains reached their maximum twenty to thirty minutes after meals and were relieved by taking food or soda. Except for some dental infection, physical examination revealed nothing of significance. Roentgenologic investigation disclosed the presence of an ulcer on the posterior wall of the stomach near the lesser curvature and just above the angle, as well as of a duodenal ulcer.

The patient elected to try a medical regimen for the treatment of these ulcers. She was hospitalized and given a bland type of diet, with frequent feedings of milk between meals. She was also given 60 grains of alkali and 90 grains of duodenal extract daily. Barbiturates and belladonna were used three times a day. Frequent aspiration of the gastric contents during the course of hospitalization revealed free acids ranging from 28 to 40; under stimulation with histamine total acidity reached 80 and free hydrochloric acid 68. There was definite clinical improvement; the stools after the first few days in the hospital were negative for blood, and sixteen days after treatment was begun roentgenologic investigation showed that the gastric ulcer had disappeared completely.

*Case 6.—Gastric ulcer.*—This patient, a man fifty-seven years old, stated that for three years he had had intervals of epigastric distress which had been especially troublesome in the spring and autumn. His pain was situated to the left of the midline near the costal margin, and it

reached its maximal intensity one and a half to two hours after meals. He was occasionally awakened at night, between midnight and 2 a. m. Milk and alkalis had invariably relieved the distress. In the six months preceding admission to this Clinic the distress had been more severe and had been less amenable to the usual methods of obtaining relief. Determination of gastric acidity gave values of 70 for total acids and 58 for free hydrochloric acid. A roentgenogram disclosed a perforating ulcer on the posterior wall of the stomach near the lesser curvature and just above the angle.

The patient elected to try a medical regimen and was hospitalized. He was placed on a bland diet and given 60 grains of alkali and 90 grains of duodenal extract daily. In addition, he was given barbiturates and atropine twice daily, and 1 ounce of olive oil at 9 p. m. His improvement was very prompt and, after eight days' hospitalization, another roentgenogram of the stomach was taken. At that time the ulcer on the lesser curvature of the stomach had almost completely disappeared. Because of financial reasons, however, it was impossible for the patient to remain any longer for treatment.

Examinations of the stool were persistently negative for blood. The patient was advised to continue on this regimen and to report for reexamination after three weeks.

*Case 7.—Recurring duodenal ulcer following a Billroth I operation.*—A man, thirty-four years old, had begun having indigestion five years prior to his admission to this Clinic. The distress was in the midepigastrium and reached its maximal intensity from one and a half to two hours after eating. The use of soda usually would promptly relieve the symptoms. At intervals the patient had been nauseated and occasionally he had vomited. He was examined at this Clinic and found to have multiple duodenal ulcers.

Estimation of gastric contents gave values of 88 for total acidity and 78 for free hydrochloric acid; 160 c. c. were aspirated. At operation this patient was found to have multiple duodenal ulcers with diffuse duodenitis. Partial duodenectomy, partial gastrectomy, a Billroth I type of operation was performed. His convalescence was without incident. He remained well for about five months, when recurring indigestion developed, with symptoms similar to those for which he was operated on.

The patient returned for examination and on roentgenologic investigation was found to have recurring ulcer at the site of the anastomosis. Estimation of the gastric contents following the use of histamine showed a maximum of 61 for total acids and 58 for free hydrochloric acid. A correct reading was not obtainable because all of the specimens recovered contained bile. The patient was hospitalized and placed on a bland diet, the amount of which was gradually increased, he was given 90 grains of alkali and 90 grains of duodenal extract daily. Additionally, he was given barbiturates and atropine four times daily. One infected tooth was removed. He gradually improved. A roentgenogram taken four weeks after the onset of treatment showed complete disappearance of the ulcer niche.

*Case 8.—Recurring duodenal ulcer following a Billroth I type operation.*—This patient, a man aged forty, stated that he had begun to have indigestion at the age of twelve. Even at that early age there had been some suggestion that he had a peptic ulcer. At the age of seventeen, a diagnosis of peptic ulcer had been made, and he had been put on Sippy treatment with temporary cessation of symptoms. At intervals following this he had experienced indigestion, and by the time he had reached twenty-nine he was having severe and debilitating digestive disturbances. The distress which, previously, had come several hours after meals and had been relieved by food and soda, now had become constant and less amenable to the accustomed methods of obtaining relief. Finally, the ulcer had perforated, and it had been necessary to perform an emergency operation, at which time a purse-string suture had

been applied to the ulcerated region. Two years later the ulcer had given him so much trouble that it was necessary to operate again. A posterior gastro-enterostomy had then been performed. Following this the patient had been perfectly well for two years, whereupon recurring indigestion had appeared which had many of the characteristics noted previously. In addition to the epigastric distress, he experienced pain to the left of the umbilicus, and this pain was projected downward to the testis. The distress came on several hours after meals and was relieved by soda.

On three occasions the ulcer had bled profusely. In August, 1934, the patient was reexamined at this Clinic, and he was found to have an ulcer on the anterior wall of the gastro-enteric stoma. Partial gastrectomy, partial duodenectomy, a Billroth I type of anastomosis, was performed. His convalescence was without incident. Very soon following this operation, however, he was again having trouble with his stomach. Again the syndrome was that usually experienced by patients with peptic ulcer. He returned for examination five months after the operation. Roentgenologic examination revealed the presence of a recurring ulcer at the gastroduodenal anastomosis. He was hospitalized, put on a bland diet, and given 60 grains of alkali and 90 grains of duodenal extract daily. In addition, barbiturates and atropine were given three times a day. He improved promptly. After fourteen days had passed he was reexamined fluoroscopically and the niche previously demonstrated at the site of anastomosis had disappeared completely.

#### COMMENT

It will be noted from a review of these histories that the treatment instituted for these patients represents a combination of various methods already generally found useful in the therapeutics of ulcer.

The general plan of diet is that so effectively used by Sippy and his colleagues. Instead of very gradually increasing the amount of food taken, however, this was increased rapidly, so that after four or five days the patients were taking a rather liberal diet, such as that usually given patients on ambulatory regimens.

The usefulness of alkalies in the control of the symptoms of peptic lesions is one of the established principles of ulcer therapy. The reduction of acidity will probably always remain one of the principles about which the treatment of ulcer must be built. Large amounts of alkali were not used. I believe that moderate amounts of soda, calcium, or magnesia have a well merited place in the therapeutics of ulcer. The use of sedatives and belladonna has been continued in the belief that the treatment of ulcer is facilitated. Whenever possible the scrupulous removal of foci of infection is advised.

It is not expected that the extract of duodenal mucosa and submucosa will prove to be a specific for peptic ulcer, for I do not believe that any single substance will ever be able to correct all the interacting factors responsible for the genesis and chronicity of this disease. I am fully convinced, however, that if some of the protecting mechanisms inherent in duodenal mucosa and submucosa could be assimilated and maintained in an extract made from these tissues, such a substance would be invaluable in the treatment of ulcer. It has not been definitely proved if these desirable qualities are preserved in the extract which has been used at this Clinic. Furthermore, such a substance, when given orally, may be inert, although experimental work now being carried out gives evidence to the contrary.



In spite of the fact that some very encouraging results were noticeable in many of the cases in which patients were treated with the extract, no conclusive deductions can as yet be made. Further experimental work and a much longer period of observation are necessary before it can be assumed that this method of treatment has any merit whatsoever.

The treatment of peptic ulcer should take into con-

sideration not only the control of the aggressive mechanism of gastric acids, but, and equally important, the support of tissue defense as well.

When the specific factors utilized by duodenal tissues in preventing erosion by acid chyme are identified and isolated, there will undoubtedly be made available a substance of great usefulness in the treatment and in the prevention of recurrences of peptic ulcer.

## REFERENCES

1. Baker, C. P.: Personal Communication to the author.
2. Florey, H. W. and Harding, H. E.: The function of Brunner's glands and the pyloric end of the stomach. *Jour. Path. and Bacteriol.* 37 :431-453 (Nov.) 1933.
3. Hoerner, M. T.: The resection of the duodenal contents after evulsion of the pancreatic ducts (Unpublished data).
4. Ivy, A. C.: Enterogastrone. *Modern Med.*, 3:22, (Feb.) 1935.
5. Kosaka, T.; Lim, R. R. S.; Ling, S. M., and Lui, A. C.: On mechanism of inhibition of gastric secretion by fat. *Chinese Jour. Phys.* 6 :107-126 (Feb. 15) 1932.
6. Mann, F. C. and Bollman, J. L.: Experimentally produced peptic ulcers: development and treatment. *J. A. M. A.* 99 :1576-1582 (Nov. 5) 1932.
7. Mann, F. C. and Kawamura, Kyoichi: Duodenectomy: an experimental study. *Ann. Surg.* 775 :208-220 (Feb.) 1922.
8. Mann, F. C. and Williamson, C. S.: The experimental production of peptic ulcer. *Ann. Surg.* 77 :409-422 (Apr.) 1923.
9. McRoberts, J. W.: The reaction of the duodenal contents in bile fistula in animals. (Unpublished data).
10. Rivers, A. B.: Clinical consideration of the etiology of peptic ulcer. *Arch. Int. Med.* 53 :97-119 (Jan.) 1934.
11. Rivers, A. B.: Extract of duodenal mucosa and submucosa in the treatment of peptic ulcer: preliminary report. *Proc. Staff Meetings of Mayo Clinic.* 9 :663-664 (Oct. 31) 1934.
12. Stevens, G. A.: The capacity of the duodenum to neutralize and buffer acid. (Thesis).

## ABSTRACTS

DAVID, U. C.

*The Treatment of Carcinoma at the Rectosigmoid Junction by Obstruction Resection. S. G. and O. Vol. LIX, No. 3, Sept., 1934, pp. 491-495.*

The author proposes and describes an operation for carcinoma of the recto-sigmoid, less radical and less widely applicable than some others but having the advantage of removal of the growth, and adjacent lymphatics, with final restoration of continuity of the bowel. This operation is applicable in cases in which the only palpable metastases are immediately adjacent to the growth. In a limited number of cases in which it is not certain whether the lesion is benign or malignant this operation is applicable.

Assuming that in Trendelenburg position a mid-line incision has been made and the lesion found at the recto-sigmoid junction, the left leaf of the mesentery of the sigmoid and rectum is opened, and the incision carried forward at the lower end of the cul-de-sac between the bladder and the rectum to join another incision through the peritoneum on the medial surface of the mesosigmoid and mesorectum. The bowel is now pulled toward the mid-line, and the peritoneum dissected away from the mesentery by blunt dissection. The rectum is freed from the bladder by blunt dissection. The hand is now placed behind the superior hemorrhoidal vessels and the rectum freed from the hollow of the sacrum. After these maneuvers it is possible to lift the bowel containing the growth well out of the pelvis. At this point one should sum up the situation keeping in mind that it will be necessary (1) to remove the growth and its mesentery, (2) to have two or three inches of peritonealized bowel below the site of resection, (3) to cover the denuded bowel in the cul-de-sac, and (4) to have a long enough loop of sigmoid to swing around and sew to the peritoneum covered rectum for a future anastomosis. If any of these postulates are not feasible of performance, the operation proposed should be abandoned. If conditions are favorable it is easy to raise the peritoneum on either side of the cul-de-sac, and suture it to the peritoneum of the rectum. The mesentery of the bowel to be resected is divided in the usual way. The portion of the sigmoid just above the point of resection is placed in contact with the rectum just below the

point of resection and sutured to it. The parietal peritoneum is now separated from the anterior abdominal wall so that it falls without tension to the posterior parietal peritoneum. The anterior parietal peritoneum is now sutured to the posterior parietal peritoneum obliterating the cul-de-sac and extraperitonealizing the proposed site of resection. The obstructive resection as described by Rankin is now carried out, and the abdominal wall closed in layers. The clamps are removed on the following day, and a spur crushing clamp applied. If, after three months, the continuity of the bowel has not been established, the ends of the bowel, where they are not in union, are mobilized, and a three layer suture carried out.

The author has employed this technique eight times during the last ten years and has obtained very satisfactory results. Five figures accompany the article.

Nelson M. Percy, Chicago.

HUGH H. TROUT.

*The Treatment of Perforated "Peptic" Ulcers. Journal of the A. M. A., 104:1, Jan. 5, 1935.*

A study of forty-one cases of acute perforation of peptic ulcers treated by immediate operation is presented. The study was undertaken to determine:

1. The advisability of drainage after closure of the perforation;
2. The advisability of immediate gastro-enterostomy following closure of the perforation;
3. The best treatment of a gastric ulcer on the posterior wall that has perforated and is associated with hemorrhage.

The conclusions the author reaches are these:

1. Drainage following closure of a perforated ulcer should be avoided if possible;
2. Gastric suction through a nasal tube carried on continuously will decrease the necessity of immediate gastro-enterostomy. The less that is done outside of simple closure the better the patient's chances for recovery has been noted in the majority of instances, and
3. The combination of perforation with massive gastric hemorrhage of a posterior wall gastric ulcer is best treated by partial gastric resection.

Francis D. Murphy, Milwaukee.

## SECTION VII—*Surgery of the Lower Colon and Rectum*

### The Modern Proctologic Clinic\*

By

MARTIN J. SYNNOTT, M.A., M.D., F.A.C.P.  
NEW YORK CITY, NEW YORK

**P**ROCTOLOGY and procto-enterology constitute such a comparatively new specialty that there are not more than one hundred and fifty thoroughly qualified proctologists in the whole United States. Until quite recently our medical schools have given but little instruction in this subject, and even today the young men who graduate from our great medical centers receive no real training in the diagnosis of rectal diseases and their knowledge of the subject is surprisingly meager. A questionnaire (1), sent by H. Z. Hirschman in 1933 to every medical school in the United States, Canada, and the Philippines elicited the information that only twelve have adequate courses in proctology. Twenty-three schools have separate out-patient clinics but the Proctologic Department is combined with or is a division of that of Surgery; in fifty-three the teaching of proctology is combined with surgery and there is no separate out-patient clinic.

Very few hospitals, even in the largest cities, have proctologic clinics; for instance, in New York City there are only four such clinics officially listed and approved by the Academy of Medicine and the New York County Medical Society. In the suburban towns and smaller cities throughout the country the greatest ignorance of proctology prevails, and it is safe to say that not one percent of the medical practitioners of the United States own electrically lighted proctoscopes or would know how to use them if they did. The sigmoidoscope should, of course, be employed only by those specially trained in its use.

This situation is gradually being recognized, and many hospitals which formerly had no rectal clinics are now establishing them. Since it often happens that a new department, even though important, has difficulty in obtaining the floor space and equipment it needs and deserves, this paper is written with the idea of assisting those who may be about to start a proctologic department.

A decade or so ago, St. Mark's Hospital for Diseases of the Rectum, in London, had outgrown its quarters and the need for a new building was apparent. W. B. Gabriel, one of the attending surgeons, was delegated to draw up the plans. He devoted a year to this study with the result that the new building is a model of efficiency and convenience and is perfectly adapted for teaching. (12) The experiences of Mr. Gabriel

and his co-workers have done much to standardize the practice of proctology the world over, and the Out-Patients' Department of St. Mark's Hospital may safely be taken as a model. In reply to a recent letter inquiring whether or not any defects in the system of arrangement of the clinic had been discovered as a result of use, Mr. Gabriel writes:

"So far as the floor plan is concerned, I think the only defects which we have discovered in the process of time relate to the accommodation of patients in the Waiting Hall, which has proved too small for the large numbers which we now have to deal with; if we had our chance to do it again we should certainly have to make a larger Waiting Hall. The other little point I think relates to the actual Examination Room. We often have numbers of visitors and I think we want more room between the ends of the couches and the basins, so that nurses and visitors can circulate freely. Otherwise everything works as smoothly as ever." (2)

This is mentioned for the benefit of clinics where teaching is to be done or where many visitors are expected.

The examination room at St. Mark's has been copied by Bensuade in the Hôpital St. Antoine, in Paris, and also in our new Midtown Hospital in New York. (Fig. 2).

#### PLAN AND ARRANGEMENT OF CLINIC

Dressing room cubicles are essential and there should be two for each table so that during the examination of one patient another may be getting ready, thus preventing delay. There should also be convenient and separate lavatories and toilets for men and women. Men and women should not be taken into the examining room at the same time, for even though the cubicles ensure individual privacy the conversation between surgeon and patient is audible throughout the room and its nature is often such as to render the reason for this precaution apparent.

The Proctologic Examination Room should be as near as possible to both the Pathological Laboratory and the X-ray Department. The proximity of the former will ensure the prompt examination of smears of pus for gonococci and of feces for amebæ, etc. The X-ray Department has much in common with the Examination Room and the attending proctologist will often wish to watch the flow of barium into the colon under the fluoroscope and the appearance of the bowel after evacuation, in cases of suspected cancer, diverti-

\*Read at the 162nd Annual Meeting of the Medical Society of New Jersey, Atlantic City, May 2, 1935.  
Submitted May 3, 1935.

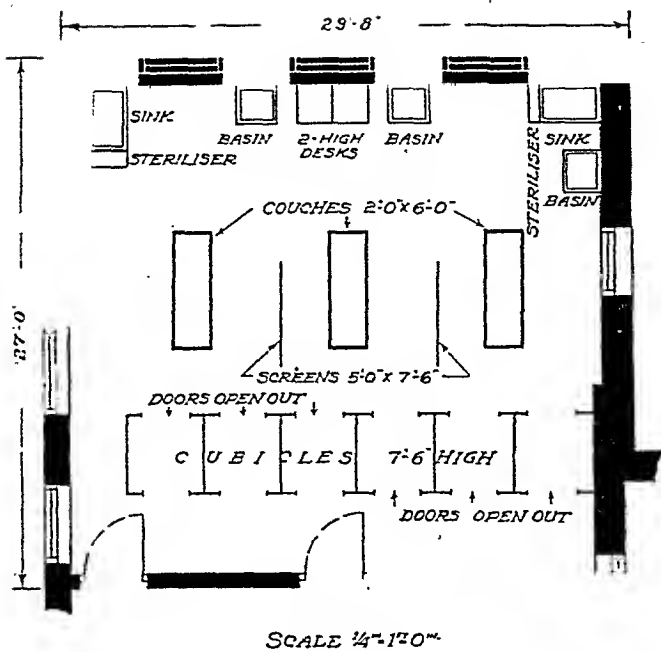


Fig. 1

culitis (13), spastic colitis, ulcerative colitis, and numerous other conditions (14).

The examination room should be well lighted and well ventilated. In regard to the latter we may remark, however, that contrary to the popular and widespread opinion among general practitioners, proctology need not be in any sense offensive work.

There should be a high, book-keeper's desk, double, so that two men may write, standing one on each side; this saves time and space.

The examining tables may be simple wooden couches. 2x6 feet, where the patients may be placed flat on their backs for abdominal palpation, or in the left Sims' or knee-left shoulder position for sigmoidoscopy. A tilting table, such as the Buie or Hanes, is a welcome addition to a clinic, as with it the surgeon is able quickly to invert the patient in the ideal position for thorough and efficient examination and treatment. If these special expensive tables are not available, any straight table may be used, but the tilting table greatly reduces the irksomeness and weariness of a long examination in the knee-left shoulder position.

A small room adjoining the examination room is convenient for the taking of brief histories, as it reduces the crowd in the latter and saves time. A junior assistant may be assigned to this duty. Most patients are referred to a rectal clinic by their physicians on account of some definite complaint, therefore no lengthy histories or general physical examinations are necessary, at least on the first visit (15).

Patients, including the free clinic cases, should be treated with the utmost consideration and respect; this rule should be rigidly enforced at every proctologic clinic.

If the clinic is conducted as a philanthropy, the hours should, for economic reasons, be in the late afternoon (from 3 to 5:30) so that the wage earners may take advantage of them with minimum loss of time from work.

#### ESSENTIAL ARMAMENTARIUM

The essential for all rectal instruments is good illumination. The proximal light is preferable, be-

Fig. 1. Floor plan of examination room, Out Patient Department, St. Mark's Hospital, London, England.

cause the very small distal lights burn out easily and, as they are costly; this is an important consideration. In our opinion the best types of sigmoidoscopes are the Yeomans, the Cameron and the Lynch. Occasionally a sigmoidoscope with small diameter ( $\frac{5}{8}$  inch instead of the regulation  $\frac{7}{8}$  inch size) like the Lyon and Bartle, is of advantage especially in work with children or with patients where there is spasm or sharp angulation at the recto-sigmoid junction. The most practical anoscope for clinic purposes is the small Kelly ( $\frac{3}{4}$  inch diameter).

No one should attempt sigmoidoscopy who is not thoroughly familiar with the procedure, or fatal injury to the patient may result. Where the bowel passes over the promontory of the sacrum the mesentery is short, and when it is put on the stretch by the instrument the patient almost always complains of momentary pain. If any unusual difficulty is encountered or if the patient cries out with pain, the operator must be most cautious as there is danger of rupturing the bowel at this point. For the same reason the sigmoidoscope used should not be more than 10 inches long, as in all probability the end of a longer instrument is merely putting a loop of the sigmoid on the stretch and is not in the descending colon, as the inexperienced proctologist may be led to believe. We have seen two cases of ruptured sigmoid as a result of instrumentation, both accidents occurring in the practices of able and experienced proctologists. In one instance the rupture was not recognized at the time, and the patient died a few days later of septic peritonitis. In the second case, the rupture was due to an attempt to use a very long (16 inch) sigmoidoscope. This rupture was promptly recognized, an operation was performed within a few hours, and the patient made an uninterrupted recovery.

A good suction machine is almost indispensable, as with it pus, blood, mucus, and liquid feces may be quickly removed, allowing thorough inspection of the mucosa of the rectal ampulla and lower sigmoid. It also disposes of the smoke during electrocoagulation or surgical diathermy or during the use of the Paquelin cautery.

Another essential is a modern machine for electrocoagulation and cutting. Formerly many minor surgical procedures required hospitalization because of the danger of postoperative bleeding; these may now be done in the clinic, for there is little danger of hemorrhage after properly performed electrosurgery. Electrocoagulation or the electrical cutting current is very useful in the removal of polyps, and certain types of adenocarcinoma may be successfully treated by this method.

*Case.* Mrs. F. A. C., widow, aged 58, came to us first in 1931. She had noticed blood in stools since 1929, and had been treated for piles by several general practitioners. She finally consulted a general surgeon who recognized the true nature of her trouble and referred her to us for treatment. Examination revealed a fungoid, cauliflower neoplasm, the size of a large English walnut, on a sessile base  $\frac{2}{3}$  inch in diameter, located one inch above the anus on the anterior rectal wall. The growth bled easily and presented the adenomatous, polypoid appearance, with ragged ulcerating surface and dirty exudate, characteristic of malignancy. Blood Wassermann was negative. A biopsy

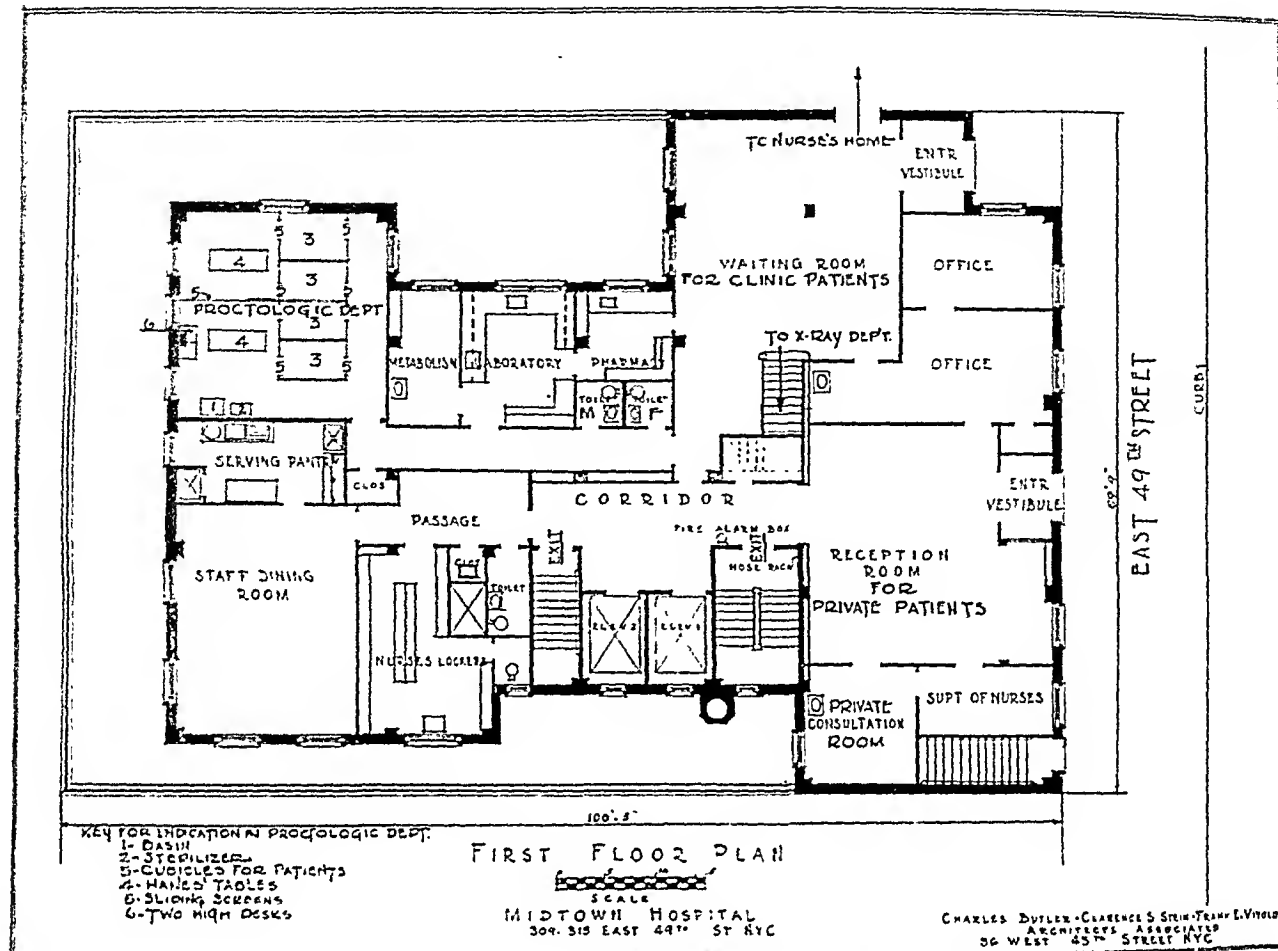


Fig. 2

was performed by Dr. Francis Carter Wood, who reported the tissue highly malignant, radio-resistant, inoperable adenocarcinoma. With the patient in the inverted position on the Hanes table, the anal sphincters were anesthetized with novocaine, and when they were relaxed, a large operating bakelite speculum  $1\frac{1}{4}$  inches in diameter was introduced and the growth was thoroughly coagulated. This procedure was repeated at intervals of a fortnight or so until 8 treatments in all had been given. No other measures were taken except to regulate the diet and keep the bowel movements soft. Bleeding ceased after the first treatment, the size of the growth rapidly declined, it finally disappeared, and the patient has been well ever since—a period of 3 years. The appearance of the mucosa is normal, the lumen of the bowel has been preserved, and no scar tissue can be felt on digital examination.

#### ANESTHESIA

In many clinic cases the anal conditions are so extremely painful that it is necessary to use an anesthetic of some kind before a thorough examination can be made. Painful fissures and ulcers, inflamed crypts, papillitis (16), pectenosis (3), and submucous abscesses often produce sphincteric anal spasm so intense that any digital or instrumental procedure is impossible. This is especially the case in highly neurasthenic or psychopathic individuals. For the relief of this condition novocaine or other local anesthetic is indicated, injected subcutaneously and into the sphincter muscles.

When silver nitrate is used in the anal region, the area is first anesthetized with local external applications of 4% cocaine or 10% metycaine solution, but cocaine is never used hypodermically.

Low spinal anesthesia is preferred for operative work such as hemorrhoidectomy, pectenotomy (4), and in fact for all surgical procedures about the anus and lower rectum. It has been proved by Gabriel and others at St. Mark's to be a safe and effective routine method (5). Lumbar puncture is sometimes followed by headache but this can be prevented in a large measure by the use of a fine needle in giving the spinal injection and by keeping the patient in the Trendelenburg position for 6 hours after the operation and not allowing the sitting posture for at least 24 hours.

We are not enthusiastic about caudal, sacral, or transsacral anesthesia, as it offers no apparent advantage over a low spinal and has a record of 20% complete or partial failures.

Local anesthetics—novocaine or anesthetic oils—may be used in operative procedures, but they sometimes alter the pathological picture, making it difficult to decide how much tissue should be removed; also the anesthesia is not always complete.

We hardly ever employ a general anesthetic because of the danger of postoperative chest complications and coughing. The vomiting and straining which frequently follow general anesthesia produce anal eversion.

prolapse of rectal mucosa with postoperative strangulation, or an annoying corona of edema, congestion or ulceration. The skin tabs which result prevent a perfect operative result and also delay convalescence.

All surgical procedures where an anesthetic is necessary will be facilitated if the patient is given a suitable dose of sodium amytal, nembutal, allonal, ortal sodium, alurate or phenobarbital the preceding night and a hypodermic injection of morphine with hyoscine one hour before the operation.

#### CONDITIONS TREATED IN A PROCTOLOGIC CLINIC

Among the many conditions which may be treated to advantage in the proctologic clinic are pruritus, amebiasis, and hemorrhoids. The clinic serves also a useful purpose in the prevention of cancer and in its early diagnosis while it is still operable.

#### PRURITUS

Many theories have been advanced concerning the etiology of pruritus. This seems to vary in different sections of the country: thus in New York comparatively few cases of fungus origin are seen, while in Richmond, Va., E. E. Terrell reports that 90% of his cases are primarily due to ringworm infection (6); on the other hand, R. A. Scarborough of San Francisco states that in 151 out of 152 cases of anal pruritus some definite local pathology was found on examination (7).

The cases of pruritus seen in our clinic during the past 5 years can be divided into four groups, according to the etiological factors, as follows:

1. *Local anal pathology.* The *anal conditions* which most frequently serve as exciting causes of pruritus are cryptitis, papillitis, pectenosis, fissure, ulcer, fistula, pin worms, submucous abscess, skin tabs from old thrombotic external hemorrhoids, prolapsing internal piles, leakage from an atonic anus due to tabes or pederasty or an incompetent sphincter following surgery or trauma. Certain of these conditions, such as painful ulcers and fissures, may be treated by palliative measures, but in many cases surgery is necessary.

2. *Intestinal toxemia* AVGQ. Under this heading we include the toxic colon (18) and infectious proctitis due to the streptococcus or the gonococcus. Pruritus may result from the toxins which are absorbed by the lymphatics and enter the connective tissue perianal spaces, causing an excitation of the sensory nerves—neurodermatitis. Such cases are helped by colon stasis regimen, bland non-roughage diet, and colon irrigations; in fact colon drainage by effective lavage is definitely beneficial. In pruritus complicating severe intestinal toxemia, duodenobiliary drainage at regular intervals, given according to the technique of B. B. Vincent Lyon (8) is of great value. This treatment will relieve the associated biliary and intestinal stasis, the chronic low grade infection of the gall tract, and the duodenitis (19).

3. *Epidermophytosis, trichophyton or other fungus infection.* The presence of fungus infection should be suspected in every case of pruritus and examination of the feet and finger nails for evidence of it is always indicated. If this is found, treatment with mercury, mercurochrome or salicylic acid according to the routine described by Terrell (6) is usually effective. Fungus antigens are helpful in obstinate cases.

4. *Diabetes.* This is a rare factor in pruritus, but it does occasionally occur. Therefore every patient, especially those who are middle aged or obese should have urinalysis and perhaps a blood sugar determination or a sugar tolerance test.

For the symptomatic relief of the itching in pruritus—irrespective of cause—we have had exceptionally good results from the injection of benacol (9), anacaine (10) or one of the other similar anesthetic oils now on the market. These oil preparations owe their efficacy to the fact that they are slowly absorbed in the tissues and therefore their effect is prolonged—the anesthesia lasting from 3 to 7 days.

We advise the violet ray or alpine sun lamp in all obstinate pruritus cases, but in our clinic the X-ray is not used. This latter method devitalizes the skin and causes connective tissue growth with thickening, hypertrophy, and radiation dermatitis, making the last state of the patient worse than the first.

Personal hygiene is always stressed: pruritic patients are instructed to take daily hot baths and to wash the anal region with a good soap and hot water after each bowel movement. If the pruritic area is unduly hairy it is shaved; certain patients do not begin to improve until this is done.

#### AMEBIASIS

Since the Chicago epidemic in the summer of 1933, many cases of amebic dysentery have been reported in various sections of the country. There are undoubtedly numerous unrecognized ambulatory cases, and physicians in gastro-intestinal and proctologic clinics should therefore be particularly alert and vigilant in recognizing and diagnosing the condition. In the subacute or "walking" types the usual complaints are blood in the stools, with rectal pain or tenesmus and tenderness along the transverse colon, the *pars descendens* or sigmoid, together with malaise and loss of working power. Prompt diagnosis and appropriate intensive treatment often produce spectacular results.

*Case.* Woman, secretary, unmarried, aged 26, living in a suburb from which she commuted daily, was referred by her family physician to the Midtown Hospital for a barium enema and plates of her colon. She had been having repeated attacks of relaxed bowel movements with occasional frank blood, and persistent rectal pain and tenesmus, for 10 weeks. The treatment had consisted of various medications, regulation of diet, etc., but no proctologic examination had been made. Our roentgenologist, Redford K. Johnson, before giving the barium enema, decided that sigmoidoscopy was indicated and brought her into the proctologic clinic. The rectum contained much mucus and feces streaked with blood. The mucosa showed the petechial spots characteristic of amebic infection; these were easily traumatized and bled at the slightest touch. There was one small serpiginous ulceration. A small, dull, spoon curette removed some of the infected material which, on examination, showed numerous endamebal histolytic. The patient was immediately given an intramuscular injection of emetine hydrochloride and a course of intensive treatment was started. She responded favorably and made an uninterrupted recovery.

#### HEMORRHOIDS

It requires a long clinical experience to decide upon the proper method of treating hemorrhoids. The three methods used in our clinic are:

1. *Injection.* This is employed only in cases of uncomplicated internal hemorrhoids—those which are soft and bleed easily. We use a mixture of 5% phenol

in oil which, when properly injected, gives most satisfactory results. Even cases so severe as to appear, at first sight, unsuited to this method often respond favorably.

2. *Operation.* This is necessary if the piles are large and prolapsed. The Buie technique is followed with the exception of position: we adopt the exaggerated lithotomy position, whereas Buie places the patient prone, face down, with an elevated bridge under the pelvis.

3. *Expectant.* By this is meant rest in bed, hot baths, local sedative or astringent applications, non-roughage diet and colon regimen. It is indicated in the case of feeble or elderly persons who are debilitated or who have weak hearts.

We make it a rule never to operate in the presence of strangulation, perianal edema, ulceration or sloughing. In such cases expectant treatment alone is indicated, with the possibility of operation later. Failure to observe this rule may result in grave complications, septicemia and death.

*Case.* Young man, chauffeur, came for advice about "piles." Examination showed large, prolapsing, internal hemorrhoids, not inflamed. Operation was advised. Ten days later he returned in great discomfort, reporting that his employer had sent him to a general hospital where the attending surgeon had turned him over to an interne for operation. He had been discharged "cured" on the fourth postoperative day. We examined him again and found an enormous perianal corona of edema due to prolapsing, constricted internal hemorrhoids and rectal mucosa. We advised him to return to the hospital for further care, which he did. This time an assistant attending surgeon, not a proctologist, decided to operate at once instead of ordering palliative treatment; i.e., hot sitz baths, local sedative moist dressings, rest in bed and suitable diet. The anus was divulsed and an attempt was made to excise the prolapsing edematous and highly inflamed tissue. The patient developed fever, rapidly became septic, the blood culture showed streptococci, and he died a few days later of septicemia.

#### CANCER. EARLY DIAGNOSIS AND PREVENTION

The greatest object in proctology today is to facilitate the diagnosis of malignant growths and to recognize pre-cancerous conditions, such as adenoma and polyp, thus permitting cancer to be attacked at an early stage.

No treatment of hemorrhoids, operative or otherwise, should be undertaken without a thorough and satisfactory examination of the lower sigmoid, anus and rectum.

The history of most clinic patients who come to us with advanced carcinoma is one of neglect and delay; a history of bleeding for 6 to 12 or even 18 months; a diagnosis of "piles" by the family physician, and treatment by suppositories and ointments. Of the new cases of cancer seen at proctologic clinics, 40% are inoperable, and 20% give a history of hemorrhoidectomy mistakenly performed without preliminary sigmoidoscopy within 6 months or a year. The general practitioner must learn to recognize the symptoms of rectal cancer before the growth has become inoperable. A history of bleeding from the rectum or of blood streaked stools, rectal irritability, mucoid discharge, or alteration in the regular habits of defecation should

always suggest a thorough proctologic examination by a qualified specialist equipped with the necessary, properly lighted instruments.

The hard nodules of an early anal epithelioma, which bleed easily after a bowel movement, are sometimes mistaken by general surgeons inexperienced in proctology for "bleeding piles," and ill-advised surgical procedures undertaken.

*Case.* Women, aged 42, married and mother of one child, came to our clinic with the following history. Four weeks previously she had had a Whitehead operation for piles, performed by a general surgeon. Before this she had suffered from anal pain and spasm, with occasional bleeding for 9 months. She did well immediately after the operation, but a week later the surgeon informed her husband that the laboratory sections of the tissue removed indicated malignancy. Examination showed an evident recurrence of the growth, as there were numerous hard nodules in the line of the incision. A proctologic surgeon was called in consultation and a perineal excision of the anus and rectum performed. She made an excellent post-operative recovery and remained in good health for a year, when metastases suddenly developed in the brain and she died.

Polyps are not uncommon in young children and often cause bleeding. Children submit readily, as a rule, to rectal examinations if their confidence and co-operation are secured, and sigmoidoscopy is relatively easier in a child than in the average adult.

*Case.* Boy, aged 6, was brought to us by his mother with a history of bright blood in his stools for 6 months. She had taken him to several pediatric clinics, where medicine and special diets were prescribed for "hemorrhagic colitis," but no rectal examination had been suggested or performed. Sigmoidoscopy showed a bleeding polyp on a pedunculated base,  $\frac{3}{4}$  inch in length, in his rectum. A Yeomans electrocoagulating snare was passed about it, through a bakelite speculum, and the growth removed. The patient felt no pain and has been without symptoms for a year.

#### CONCLUSIONS

In conclusion, it may be stated that there are no short cuts into the field of proctology. A thorough knowledge of gastro-enterology is a necessary prerequisite and familiarity with the pelvic and perineal anatomy is essential. Sound judgment in diagnosis and treatment is acquired only after extensive experience, and to qualify as a specialist many years of painstaking study, travel and observation are required. The functions and mechanics of the muscles, glands, nerves and blood vessels in health and disease must be understood.

Preliminary training in general surgery is most desirable, if not obligatory. It is *not* necessary, however, for every proctologist to feel that he must be qualified to perform abdomino-perineal excision for carcinoma. This operation had better be left to those surgeons—few in number—who, as a result of experience, opportunity and training have acquired the skill, technique, dexterity, speed, team work, and special knowledge essential to success and to a low operative mortality. This includes the careful and intelligent pre-operative preparation of the patient and the after treatment.

#### REFERENCES

1. Hirschman, H. Z.: Report for the Committee on Teaching of Proctology. *Tr. Am. Proct. Soc.*, 35, p. xx, 1934.
2. Gabriel, W. B.: Personal communication to the author, Oct. 25, 1934.



3. Abel, A. L.: The pecten: the pecten band: pectenosis and pectenotomy. *Lancet*, 1:714-718, 1932.
4. Mechling, C. C.: Some comments on pectenosis. *Tr. Am. Proct. Soc.*, 34:41-44, 1933.
5. Gabriel, W. B.: Recent advances in the treatment of rectal diseases. *Practitioner*, 133:489-509, 1934.
6. Terrell, E. H.: Pruritus ani. *Bull. Stuart Circle Hosp., Richmond, Va.*, 4:64-68, 1934.
7. Scarborough, R. A.: Pruritus ani: its etiology and treatment. *Ann. Surg.*, 98:1039-1045, 1933.
8. Lyon, B. B. V.: Non-surgical drainage of the gall tract . . . *Phil. Lea & Febiger*, 1923.
9. Ycomans, F. G.; Gorsch, R. V., and Mathesheimer, J. L.: Benacol in the treatment of pruritus ani. *Tr. Am. Proct. Soc.*, 28:24-29, 1927.
10. Gorsch, R. V.: Oil soluble anesthetics in proctology. *M. Rec.*, 139:35-38, 1934.
11. Buie, L. A.: Proctoscopic examination and the treatment of hemorrhoids and anal pruritus. *Phil. Saunders*, 1931.
12. Synnott, M. J.: Proctology in America and abroad. *M. J. and Rec.*, 129:49-109, 1929.
13. Idem: Diverticulitis. *Tr. Am. Proct. Soc.*, 34:140-147, 1933.
14. Idem: The examination of the abdomen. *M. J. and Rec.*, 134:435-440, 1931.
15. Idem: Brief review of modern proctology with special reference to treatment of cancer of the rectum. *M. J. and Rec.*, 135:549-555; 136:7-10, 1932.
16. Idem: Papillitis, cryptitis and pectenosis. *M. Rec.*, 139:392-394, 1934.
17. Idem: Intestinal toxemia, its diagnosis and treatment. *M. J. and Rec.*, 136:441-447, 1932.
18. Idem: The toxic colon. *M. J. and Rec.*, 131:121-129, 1930.
19. Synnott, M. J.: The diagnostic and therapeutic value of Lyon's method of non-surgical duodenobiliary drainage. *Am. J. Surg.*, 35:136-141, 1922.

## SECTION VIII—Editorial

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastroenterological Association is in no way responsible for editorial expressions.

### THE COMMON PATHOGENESIS OF TERMINAL ILEITIS, IDIOPATHIC ULCERATIVE COLITIS AND BACILLARY DYSENTERY

FELSEN'S recent alignment of regional ileitis with bacillary dysentery (*A. J. D. D. and N.*, 1-11, Jan., 1935), leads one to reconsider the trend of the last four or five years towards the inclusion of chronic bacillary dysentery and ulcerative colitis in one class. Because of the resemblance of these two conditions perhaps the dysentery bacillus is being unduly neglected.

If we assume that these two diseases are one and the same, still there are many patients with the clinical picture of idiopathic ulcerative colitis who give positive serum agglutination reactions in high dilution with one or other strain of the dysentery bacillus. And that these strains are specific is indicated by the marked reaction to one strain and the almost complete failure of reaction to any of the other strains. The several dysentery strains would seem to be almost as specific as the strains of the pneumococcus.

In recent years, practically all of our adult cases that have reacted have given sharp agglutination reactions in high dilution with one strain only, either the Flexner or the Mt. Desert strain, mostly the latter, and only slight reactions with all the other strains. The commercial serums obtainable do not represent the Mt. Desert strain. Yet when the agglutination reactions are highly specific for a particular strain, obviously any serum or vaccine used must also be specific, and the serum or vaccine from any other strain or strains can be nothing else than useless. It is because of an occasional apparent striking result from the use of vaccines that I open the subject once more.

In order therefore to help toward conclusions as to the relation of chronic bacillary dysentery, ulcerative colitis and regional ileitis, and to appraise the therapeutic value of serum or vaccine in these chronic cases, may we urge that those clinicians and bacteriologists who are making observations test all cases of ulcerative colitis and regional ileitis for agglutination reactions with the various strains of the dysentery bacillus? May we urge further that, where such are

positive, they administer a stock vaccine of the specific strain or a serum that represents it?

In some of our clinics this has not been done, yet, until such tests and treatments are carried out consistently through the years, we cannot really establish the relation of the diseases, or assess the therapeutic value of serum or vaccine; and it may be that we are missing a valuable therapeutic help. Naturally, judgment of results will have to be reserved, for in any chronic case there cannot be the dramatic effects obtained in an acute case.

At this stage, might we not properly reclassify our cases into: Ulcerative colitis with dysentery agglutinations and Ulcerative colitis without dysentery agglutinations; and, Regional ileitis with dysentery agglutinations and Regional ileitis without dysentery agglutinations?

Walter A. Bastedo, New York City.

### NEW YORK CITY ACTIVE FOR THE AMERICAN BOARD OF GASTROENTEROLOGY

THE medical men of the city of New York comprise approximately one-twentieth of the membership of the American Medical Association. It has two active gastroenterological associations, one local to New York City, the New York City Gastroenterological Association, and the other, a newly formed national organization, the National Society for the Advancement of Gastroenterology. Both have gone on record and are actively interested in the establishment of the American Board of Gastroenterology. The resolutions from them sent to the House of Delegates of the American Medical Association are as follows:  
Adopted Jan. 31, 1935:

We, the New York Gastroenterological Association, all of whom are members of the American Medical Association in good standing, respectfully ask for favorable action on the recognition of the American Board of Gastroenterology. For eighteen years we have had a Section in the subject in the American Medical Association, which Section has stimulated an interest in the diagnostic and medical aspects of abdominal work and done much in advancing American Medicine. In this Section the workers in this field of medicine have

given of their time and activities in the constantly multiplying aspects of the subject. To encourage these, we feel that this field of work should be recognized by certification by the already established American Board of Gastroenterology.

Adopted Feb. 6, 1935:

WHEREAS, the members of the National Society for the Advancement of Gastroenterology assembled Feb. 6, 1935, which organization is committed to the advancement of gastroenterology for the benefit of American medicine, and

WHEREAS, since the establishment of the Section of Gastroenterology and Proctology eighteen years ago in the American Medical Association it has done much in stimulating a higher quality of diagnostic and medical abdominal work in the profession in this country, and

WHEREAS, most of the advances made have been accomplished by those who have been working intensively in this field of work and freely given of their work to American medicine, and

WHEREAS, the members of this organization are all of them members of the American Medical Association in good standing,

BE IT RESOLVED, that we respectfully request our parent organization, the American Medical Association, to certify this field of work by authorization of the American Board of Gastroenterology to stimulate still better work in the subject on the part of the profession and request also that we as a national organization be given representation on the Board of Gastroenterology with the Section of the American Medical Association and the American Gastroenterological Association.

It is hoped that these resolutions will assist in the establishment of the American Board of Gastroenterology so that this field of medical work can take its place in certification with the departments of ophthalmology, otolaryngology, obstetrics and gynecology, dermatology and syphilology, pediatrics, psychiatry and neurology and radiology.

Anthony Bassler, New York City.

## SECTION IX—Book Reviews

(This section is open to contributions from any medical reader, whether a member of the Editorial Council or not).

*Diet Manual, St. Mary's Hospital, Rochester, Minn.* By Sister Mary Victor, R.N., B.S., Director of the Department of Nutrition, St. Mary's Hospital; Published by the Institution; Second Edition, 1935, 191 pages, supplemented by numerous graphs and tables.

THE author is recognized as one of the outstanding clinical dietitians and nutrition experts in the world. In her book she has performed a distinct service to hospitals and sanatoria and even to internists, generally, by rendering available the specific dieto-therapeutic regimes which have made distinguished the department which she heads at the famed St. Mary's Hospital, the "helping hand and workshop" of the Staff members at the Mayo Clinic.

Although Sister Mary Victor's book is classed as "Second Edition," the reviewer is not familiar with the "first edition," unless such term could be applied to the numerically limited and rather preciously hoarded, paper-covered "Diet Lists" of which the visitor to the Mayo Clinic occasionally caught a fleeting glimpse—and vainly endeavored to borrow, beg, buy or purloin a copy!

Evidently, in a certain degree, the economic depression affected St. Mary's Hospital. While we commiserate with the management of that Institution, simultaneously, we rejoice that the consequent lessening of routine labor made possible a "breathing spell" for a very much overburdened Sister and permitted her to set forth, in orderly sequence and in suitable form, those procedures to which she has given so many thoughtful and arduous years. The resulting book is eminently satisfactory for what it purports to be: "simply a compilation of diet procedures employed in the treatment of disease by the Medical Staff of St. Mary's Hospital and the Mayo Clinic." However, Sister Mary Victor is rather more than modest when

she states that her book is "simply a compilation." As one peruses Part 1 ("The Optimum Diet"), Part 2 (Therapeutic Diet for Adults, with its twelve sections), Part 3 (Infant and Child Feeding), Part 4 (Instruction Sheets) and Part 5 (An "Appendix" rich in details respecting various height, weight, age tables, lists of food values, qualitative, nutritive, and chemical "dissection" of specific foods and diets, etc.), he discovers that the Author has contributed much of her own knowledge and ingenuity to make clinically workable the demands—both investigative and therapeutic—of an exacting, ever-revising, inquisitive group of clinicians and researchers. In these days of nutritional flux, one wonders when the Director of a Department of Diets in a Clinic whose attitude is almost as much in the field of research as in medical and dietetic therapy, finds conditions sufficiently "static" to admit of having any routine or set scheme of dietetics in her plant. Certainly, one so placed, often must needs herself resort to the principles of the ketogenic diet for the resultant headaches!

Without going into intricate analysis of the "compilation" presented by Sister Mary Victor—really an encyclopedia of what is most advanced and proved in the modern conception of diet as a means of treating common or unusual ailments—one cheerfully commends the *rationale* and clarity of the diets set forth for the management of constipation, weight reduction, cardiovascular and renal disease, diabetes (with its excellent recipes), peptic ulcer, ailments of the colon, (particularly the ulcerative affections), arthritis, the ketoses, postoperative conditions, and those suited to ailments affecting infants and children.

The methods of presentation are simple and logical. Diets are exhibited to meet all possible variations in given affections and, what especially is satisfying, is that more than an ordinary effort has been made to

offer selections of foods which readily are available in most communities, are economical and are palatable.

"Instruction Sheets" for patients' use are refreshingly simple in that they state definitely what patients may have and what not, thus affording those employing them such choices as may suit the purse, residence or social condition. Faddism and the exhibition of "queer," "patented," "foreign," expensive or difficult-to-secure foods rarely. Whether patients remain for treatment at Rochester or, after being set on the proper trail, they continue dietotherapy at home, the very sensible instruction-sheets presented by Sister Mary Victor, if adhered to, cannot fail to prove helpful.

The Author is to be congratulated upon her accu-

ate, intelligent and painstaking work. Without reservations, her book is recommended to dietitians in hospitals and sanatoria as the most useful compendium of its type yet published. No institution which assumes to exhibit modern dietotherapy can claim completeness unless it has available for daily use Sister Mary Victor's book. Nurses' Training Schools, nurses and physicians in practice will find the work invaluable.

The volume is attractively printed and substantially bound. Evidently it is printed privately, inasmuch as it carries no publisher's imprint other than "St. Mary's Hospital, Rochester, Minn." Presumably the book can be purchased (price not stated) by direct application to the Hospital which sponsors it.

Frank Smithies.

## SECTION XI—*Societies, Programs and Proceedings*

FINAL PROGRAM OF THE THIRTY-EIGHTH ANNUAL MEETING OF THE

### American Gastro-Enterological Association

To be held at

ATLANTIC CITY

MONDAY AND TUESDAY, JUNE 10 AND 11, 1935

HEADQUARTERS AND ALL SESSIONS AT

HOTEL TRAYMORE

MONDAY, JUNE 10, 1935

MORNING SESSION, 9:00 A. M.

Memorial Address on Dr. Albert Bernheim

Dr. David Riesman, Philadelphia.

Presidential Address

Dr. B. B. Vincent Lyon, Philadelphia.

1. "Studies on Crystalline Vitamin B—Observations in Diabetes."

Dr. Martin G. Vorhaus, New York, N. Y.

R. R. Williams, M.S. (by invitation),  
New York, N. Y.

R. E. Waterman, B.S. (by invitation),  
New York, N. Y.

DISCUSSION to be opened by

Dr. Joseph T. Beardwood, Jr., (by invitation), Philadelphia, Pa.

Dr. J. Earl Thomas, Philadelphia, Pa.

2. "Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes."

Dr. T. L. Althausen, San Francisco, Calif.

B. Blomquist, M.A., (by invitation),  
San Francisco, Calif.

DISCUSSION to be opened by

Dr. Arnold R. Rich, (by invitation),  
Baltimore, Md.

Dr. Frank C. Mann, Rochester, Minn.

3. "Gastro-intestinal Manifestations of Hyperinsulinism."

Dr. Seale Harris, Birmingham, Alabama.

DISCUSSION to be opened by

Dr. Julius Friedenwald, Baltimore, Md.

Dr. Frank Smithies, Chicago, Ill.

4. "Present Conceptions of Calcium Metabolism."

Dr. David L. Thomson, (by invitation),  
Montreal, Canada.

DISCUSSION to be opened by

Dr. Lay Martin, Baltimore, Md.

Dr. A. C. Ivy, Chicago, Ill.

11:30 A. M.

5. THE ALVAREZ LECTURE—(Founded in 1928 by Dr. Frank Smithies).

Dr. Lewellys F. Barker, Baltimore, Md.

LUNCHEON

AFTERNOON SESSION

2 P. M.

6. "Abdominal Pain as a Misleading Symptom of Spinal Cord Lesions."

Dr. Everett D. Kiefer, Boston, Mass.

DISCUSSION to be opened by

Dr. Howard F. Shattuck, New York, N. Y.

Dr. Gilbert Horrax, (by invitation),  
Boston, Mass.

7. "Experimental Studies of Chronic Visceral Infection in Relation to Gastro-Enterological Problems."

Dr. Martin E. Rehfuss, Philadelphia, Pa.

Dr. Guy M. Nelson, (by invitation),  
Philadelphia, Pa.

DISCUSSION to be opened by

Dr. Ernest H. Gaither, Baltimore, Md.

Dr. W. L. Palmer, Chicago, Ill.

8. "The Present Status of Colon Bacillus Vaccine Therapy."

Dr. John G. Mateer, Detroit, Michigan.

Dr. James I. Baltz, Dr. James Fitzgerald and

Dr. Harris L. Woodburne, (by invitation),  
Detroit, Michigan.

DISCUSSION to be opened by

Dr. Sara M. Jordan, Boston, Mass.

Dr. Leon Schiff, Cincinnati, Ohio.

9. "Serum Lipase: Its Diagnostic Value."

Dr. Mandred W. Comfort, Rochester, Minn.

DISCUSSION to be opened by

Dr. Daniel N. Silverman, New Orleans, La.

Dr. Arthur C. Clasen, Kansas City, Mo.

10. "Report of Enzyme Committee."

Dr. A. H. Aaron, Chairman

Dr. H. L. Bockus

Dr. Mandred W. Comfort

Dr. Burrill B. Crohn

Dr. A. C. Ivy

Dr. Victor C. Myers

Dr. T. L. Althausen

Dr. R. H. M. Hardisty

EXECUTIVE SESSION

(Associate members are requested not to attend).

ANNUAL DINNER, 7:30 P. M.

HOTEL TRAYMORE, ATLANTIC CITY,  
N. J.

Guests of Honor

"Historical Review of Gastric Surgery"

DR. DEAN LEWIS

Professor of Surgery, Johns Hopkins University, Baltimore, Md.

"Medicine in the Eighteenth Century as seen in the Pictures of William Hogarth."

Dr. L. J. Austin, F.R.C.S.

Professor of Surgery, Queen's University, Kingston, Ontario.

TUESDAY, JUNE 11

MORNING SESSION, 9:15 A. M.

11. "Traumas Resulting From Sigmoid Manipulations."

Dr. Burrill B. Crohn, New York, N. Y.

Dr. Bernard D. Rosenak, (by invitation),  
New York, N. Y.

DISCUSSION to be opened by

Dr. Richard Lewisohn, New York, N. Y.

Dr. Charles Gordon Heyd, New York, N. Y.

12. "The Cause of Faulty Digestion After Removal of the Stomach."

Dr. Edward S. Emery, Jr., Boston, Mass.

DISCUSSION to be opened by

Dr. Franklin W. White, Boston, Mass.

Dr. Leon Bloeh, Chicago, Ill.

13. "Experimental Studies in Gastric Physiology in Man. III. The Motor Function of the Operated Stomach."

Dr. Harry Shay, Philadelphia, Pa.

Dr. J. Gershon Cohen, (by invitation),  
Philadelphia, Pa.

DISCUSSION to be opened by

Dr. John P. Quigley, Cleveland, Ohio.

Dr. M. J. Wilson, (by invitation),  
Toronto, Canada.

14. "Observations on Ulcerations Adjacent to Experimental Gastric Pouches in Dogs—a Preliminary Communication."

Dr. Asher Winkelstein, New York, N. Y.

DISCUSSION to be opened by

Dr. A. C. Ivy, Chicago, Ill.

Dr. Boris P. Babkin, Montreal, Canada.

15. "Gastroscopy with a Flexible Gastroscope."

Dr. Rudolf Seindler, (by invitation),  
Chicago, Ill.

DISCUSSION to be opened by

Dr. Chevalier Jackson, (by invitation),  
Philadelphia, Pa.

Dr. William A. Swalm, Philadelphia, Pa.

16. "Gastric Syphilis."

Dr. Clement R. Jones, Pittsburgh, Pa.

DISCUSSION to be opened by

Dr. H. L. Bockus, Philadelphia, Pa.

Dr. Albert F. R. Andresen, Brooklyn, N. Y.

LUNCHEON

AFTERNOON SESSION

1:30 P. M.

17. "Effect of Drugs on the Isolated Colon of Man."

Dr. J. A. Barga, Rochester, Minn.

Dr. J. S. Guthrie, (by invitation),  
Rochester, Minn.

DISCUSSION to be opened by

Dr. M. B. Dreyer, (by invitation),  
Halifax, Nova Scotia.

Dr. Walter A. Basdeo, New York, N. Y.

18. "Psychogenic Factors in Ulcerative Colitis."

Dr. Albert J. Sullivan, New Haven, Conn.

DISCUSSION to be opened by

Dr. Chester M. Jones, Boston, Mass.

Dr. George E. Daniels, (by invitation),  
New York, N. Y.

19. "Obesity and Its Treatment."

Dr. Walter R. Campbell, (by invitation),  
Toronto, Canada.

DISCUSSION to be opened by

Dr. Maurice L. Tainter, (by invitation),  
San Francisco, Calif.

Dr. Arthur F. Chace, New York, N. Y.

20. "Experiences With Postoperative Jejunal Ulcer and Gastrojejunocolic Fistula."

Dr. Frank H. Lahey, Boston, Mass.

DISCUSSION to be opened by

Dr. Paul W. Aschner, New York, N. Y.

Dr. L. J. Austin, F.R.C.S., (by invitation).  
Kingston, Ontario.

TO BE READ BY TITLE

1. "The Absorption of Unaltered Protein from the Normal and Abnormal Gastro-Intestinal Tract,"

Dr. Irving Gray, Brooklyn, N. Y.

Dr. Matthew Walzer, (by invitation),  
Brooklyn, N. Y.

2. "Treatment of Bleeding Peptic Ulcer—An Experimental and Clinical Study."

Dr. Benjamin M. Bernstein, (by invitation),  
Brooklyn, N. Y.

3. "Personality Study in Cardiospasm: The Meaning of the Disorder From the Standpoint of Behavior."

Dr. Edward Weiss, (by invitation),  
Philadelphia, Pa.

4. "The Levulose Tolerance Test."

Dr. Stockton Kimball, Buffalo, N. Y.  
Roger S. Hubbard, Ph.D., (by invitation),  
Buffalo, N. Y.

THE MEDICAL PROFESSION IS CORDIALLY  
INVITED

## SECTION XII—"The Clinic"

### An Unusual Case of Primary Actinomycosis Involving the Mesentery of the Small Intestine\*

By

C. J. TIDMARSH, M.A., M.D., F.R.C.P.(C).  
BOSTON, MASSACHUSETTS

A REVIEW of the literature for the past ten years, including the 670 cases reported by Sanford and Voelker in 1925, reveals the fact that primary actinomycosis of the mesentery must be extremely rare. Sanford and Voelker do not mention a single case where the mesentery primarily was involved.

In regard to the mode of infection, most authors agree that very often spore forms from vegetation are introduced into the soft tissues as a result of injury by a foreign body. In the case reported below, it is interesting to note that at operation Dr. Lahey remarked that the finding indicated perforation of the small intestine by a foreign body, and on questioning the patient later she distinctly remembers having choked on a fish bone several weeks prior to the onset of her present illness.

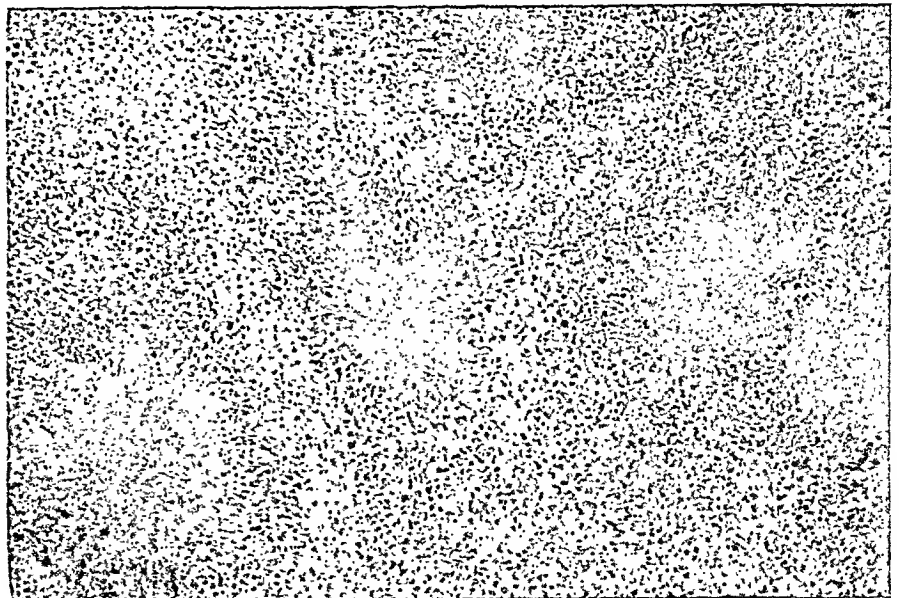


Fig. 1. Actinomycotic colonies embedded in inflammatory tissue of mesentery. Note typical ray formation. X175.

\*From the Department of Gastro-Enterology,  
Lahey Clinic, Boston, Mass.  
Submitted March 25, 1935.

## CASE REPORT

Mrs. E. T. H., housewife, age 60, was admitted to the Lahey Clinic, October 10, 1934, with complaints of: (a) full feeling in abdomen; (b) soreness left abdomen.

Present illness commenced on the 3rd of September, 1934, while enroute to Honolulu, with general malaise, loss of appetite, nausea, full feeling in abdomen, soreness in left abdomen especially when lying on left side. The ship doctor ordered salts and an enema which were partially effectual but gave no relief. During the next two days the symptoms became more severe, especially the abdominal pain, fullness and nausea. Further laxatives and enemas were not effectual. On arrival at Honolulu, the patient was admitted to the Tripler General Hospital. The following is an abstract of the hospital report:

"Admitted September 7, temperature 101°, pulse 116, respiration 22, white blood count 18,400, urine negative, blood pressure 112/64. There is a large mass the size of a coconut in the left lower abdomen—tense, not hard, tender and fixed. General physical examination otherwise negative. Daily enemas were effectual and these with turpentine stipes resulted in gradual softening of the mass with decrease in size,—mass now movable. On September 12, pelvic examination was negative with the exception of a small, cervical polyp.

Barium enema—colon essentially negative except the descending colon appears displaced toward the mid-line. Repeated the next day with same conclusion. By September 20, the temperature and white count were normal, bowels were regular and the mass estimated to be one-fifth of its size on admission. Total weight-loss ten pounds. Discharged. Final diagnosis: 1. Tumor, left lower quadrant—type undetermined. 2. Partial intestinal obstruction due to (1). 3. Cervical polyp."

Improvement continued during the return voyage. The enemas and laxatives were continued for relief of the full feeling. The patient gained four pounds. Now feels stronger but still has abdominal discomfort.

General physical examination at the Lahey Clinic essentially was negative with the exception of a small mass in the left lower quadrant towards the mid line and the cervical polyp. Laboratory examinations—urinalysis, blood count, non-protein nitrogen, bilirubin and Hinton—all normal. Gastric analysis (Ewald meal) free acid 0, total 12. X-rays of stomach and colon were negative for organic disease.

Personal and family histories irrelevant.

In view of patient's age, history achlorhydria and presence of palpable mass, exploration was advised. *Exploratory operation.*—Dr. Lahey, October 26, 1934. The liver, gall bladder, stomach, pelvic organs and

kidneys were found to be normal. The colon was normal. Adhesions in the sigmoid area and long adhesions from the small bowel over to the left lateral wall. A loop of small bowel was found to be quite reddened, with inflammatory reaction, and in the mesentery there was a hard mass, probably inflammatory, about the size of a walnut. After the mass was carefully dissected away from the small intestine, there was found at the base where it joined the small bowel, an opening from the bowel into the solid mass.

The site of injection was invaginated by two purse string sutures. Careful search throughout the abdomen revealed nothing further except the adhesions referred to above. Routine closure. The patient made an uneventful postoperative recovery.

By courtesy of Dr. Shields Warren, pathologist to the New England Deaconess Hospital, the following pathological report is given: "Several sections of the mass show irregular foci measuring as much as 1 cm. in diameter in which there is

## FOR PEPTIC ULCER

### A REVOLUTIONARY TREATMENT

*Peptic ulcer becomes symptom-free on the*  
**LAROSTIDIN TREATMENT**  
*One daily injection for about 24 days*

**Larostidin Ampuls, 5cc . . . Cartons of 6**  
*4 boxes constitute one complete treatment*

- After 5 days . . .* Pain usually disappears and does not recur. Nausea, vomiting, hyperacidity, and flatulence are relieved.
- After 10 days . . .* Normal diet well tolerated. Appetite improves. There is consequent gain in weight, general systemic improvement, and vastly improved mental outlook.
- After 24 days . . .* There is usually remission of all symptoms, viz.: food intolerance, gastric pain, and hyperacidity. Normal emptying time, normal peristalsis and absence of spasms are evidenced.

- Drs. VOLINI and McLAUGHLIN, *Medical Record*, April 17th, 1935 report: "The parenteral use of histidine monohydrochloride (larostidin, Roche) produces rapid clinical improvement in patients with gastroduodenal ulcer upon liberal diets and while ambulatory. Pain, vomiting, hypersecretion and retention quickly improve or disappear. Appetite and weight increase is noted."
- BULMER, in reporting his results in 52 cases of peptic ulcer (*The Lancet*, Dec. 8, 1934) emphasized the fact that the Larostidin treatment is better than the older methods—alkalies, feedings, etc.—in bringing about complete subsidence of symptoms, and that these results are easily achieved with ambulatory management. Dr. Bulmer's paper was abstracted in the *Journal of the American Medical Association*, February 23, 1935, page 690.

**HOFFMANN • LA ROCHE • INC • NUTLEY • NEW JERSEY**



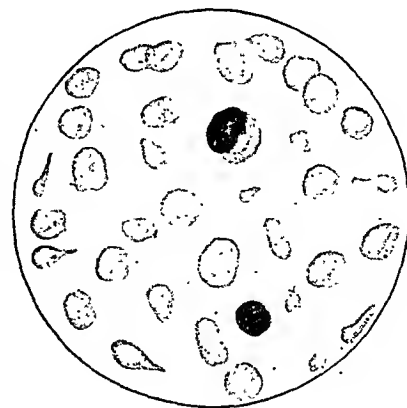
great increase in collagenous tissue. Throughout these foci are many regions of intense infiltration by lymphocytes and plasma cells. In some places, many hemosiderin-laden phagocytes are present in among the lymphocytes, and in a few foci small abscesses, with many polymorphonuclear leucocytes, are seen surrounded by a broad zone of plasma cell and lymphocytic infiltration. In the center of one such abscess are several clumps of actinomycetes with a cen-

tral mycelium and peripheral radially arranged club-like structures (Fig. 1). In the tissue surrounding the abscesses are some capillaries lined by swollen epithelial cells and in some places are seen fat laden phagocytes."

It is now nearly four months since operation and the patient reports that she is perfectly well and has no symptoms of any kind.

#### REFERENCE

Sanford and Voelker. *Arch. Surg.*, 11:809, December, 1925.



## ANNOUNCING A New Parenteral Liver Extract!

Chappel's Liver Concentrate Intramuscular, for intensive treatment of pernicious anemia.

One injection per week during relapse to obtain recovery.

One injection at two to four week intervals for maintenance.

In packages of three vials. Each vial contains 3.3 c.c. derived from 150 grams of fresh liver.

Laboratories

**CHAPPEL BROS. INC.**

Rockford, Ill.

## In Hepatic Diseases . . .

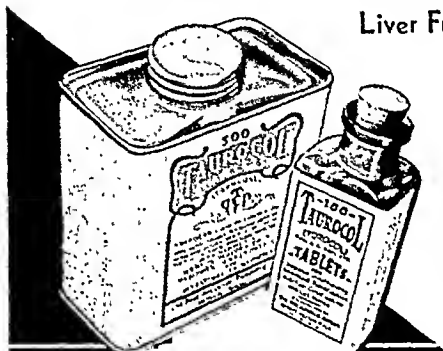
Liver Function is Best Regulated with

### TAUROCOL (TOROCOL) Bile Tablets

A RECENT CLINICAL TEST showed an average step-up of 48.3% in bile flow. The influence of bile salts was ascertained in a number of patients whose gall bladder had been removed . . . the average increase in these cases was 61.6%. Where the gall bladder was intact and functioning properly, the average increase was found to be 35%. Considering both classes of patients the average step-up was found to be 48.3%.

Samples and full information on request.

**THE PAUL PLESSNER CO.**  
DETROIT, MICHIGAN



## CELLU

### One-Three-Three Flour

*Specifically made for diets requiring a bread substitute of low available carbohydrate value*

#### Pleasant to Use

Cellu One-Three-Three Flour is carefully compounded to insure a very tasty muffin and one which is easily and successfully prepared. The flour is put up in envelopes containing a weighed portion of 45 grams, this amount being sufficient for one baking of six muffins when combined with two eggs. Patients do not tire of this bread substitute because of its pleasing flavor.

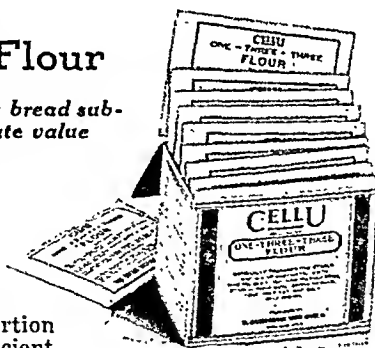
#### Ingredient Content

The chief ingredients are pulverized washed bran, starch, vegetable fat, leavening, salt, and India Gum.

*We Would Like to Send You a Sample to Try*

#### Food Value

The calculated available food value of each finished muffin is: Fat, 3 grams; Protein, 3 grams; available Carbohydrate, 1 gram.



Send me a Free Sample of Cellu One-Three-Three Flour  
and Your New Illustrated Catalogue

Name .....

Address ..... D.D.N.-5-35

**CHICAGO DIETETIC SUPPLY HOUSE**  
1750 West Van Buren Street, Chicago, Ill.

# Incomplete Intestinal Obstruction Due to Shortened Ligament of Treitz

By

JOSEPH STEIN, M.D.  
HAWTHORNE, NEW YORK

MRS. M. L. was referred on May 1, 1934, by Dr. John R. Evers for X-ray gastro-intestinal study. Her main complaints were vomiting after every meal since January and loss of weight. The vomiting came on either immediately after meals or within two hours. This patient has been previously X-rayed elsewhere with essentially negative findings reported.

The following report of my findings was sent to Dr. Evers on May 2, 1934: 'Fluoroscopic examination of the esophagus and stomach reveals momentary spasm of the cardia which, however, opens and allows the barium meal to enter the stomach; the esophagus is otherwise normal in contour. The duodenal cap is likewise momentarily spastic but soon fills out. The stomach is normal in outline.

The distal half of the descending portion of the duodenum is dilated but not permanently so as in a diverticulum. Retroperistaltic waves are observed beginning at the distal end of the descending portion of the duodenum; they are very marked. The contrast meal is reversed in direction and the reverse waves are soon observed involving the stomach right through the cardiac end filling up the esophagus in reverse direction.

X-ray films bear out fluoroscopic findings.

**Conclusions:** I consulted about this phenomenon with Dr. S. Goldfarb, chief of the X-ray intestinal division at Mt. Sinai Hospital. He advises me such a condition may be due to any of the following causes:

1. Shortened ligament of Treitz.
2. Enlarged glands pressing against the duodenum.
3. Mesenteric vessels partially occluding duodenum.
4. Functional and unknown causes.

I would suggest that you be guided accordingly."

The patient was admitted to St. Agnes Hospital, White Plains, N. Y., on May 16, 1934. The hospital records follow:

## PERSONAL HISTORY

**Chief complaints:** 1. Vomiting after every meal and pains in the abdomen following ingestion of food or water for 5-6 months.

Submitted February 20, 1935.

2. Loss of 20 pounds in weight last 6-8 months. Appetite is good but is unable to keep food down.

3. Attacks of "indigestion" with pain in the abdomen and occasional fainting during the last 20 years at irregular intervals according to the patient by eating certain foods, as corn and bananas.

**Childhood:** Chicken pox, mumps, measles and nose bleeds often.

**Surgical:** Appendectomy and hysterectomy 7 years ago. Thyroidectomy January, 1934.

**Veneral:** Denied.

**Menstruation:** 16x28x5 always regular until about 9 years ago when patient had menorrhagia (18 days) and noticed intraabdominal tumor.

**Obstetrical:** No children, no miscarriages.

## PHYSICAL EXAMINATION

**Head and Neck:** Eyes react to light and accommodation. E.N.T. negative.

**Chest:** Normal contour and expansion. Lungs clear throughout. Heart apparently normal.

**Abdomen:** Slight distension and tenderness throughout and especially in epigastrium, no palpable mass. Pelvic not done.

**Extremities:** No edema, reflexes normal.

## Laboratory Findings:

1. Urine: Negative except for very faint trace of albumin.

2. Blood: Hemoglobin 87; red blood count 4,190,000; leucocytes 15,900; small lymphocytes 10; polys 90.

May 16, 1934: From Progress Record.

Thirty-five year old white female admitted with a long history of vomiting and abdominal pains following several operations.

**Impression:** Partial intestinal obstruction and post-operative adhesions. —Dr. Byers.

May 17, 1934. Operative procedure and findings by Dr. Evers.

Rather marked adhesions of the omentum and 2 loops of small intestine along prior sub-umbilical wound. There were several peri-sigmoidal and pericecal filamentous adhesions and one loop of small intestine was angulated on itself by reason of adhesion; one apparently omental variant was found between the fundus of the gall-bladder

and the second portion of the duodenum and several small contracted adhesions overlying the second portion of the duodenum. At the ligament of Treitz there was a dense contracted band causing sharp angulation of the beginning of the jejunum. Previous appendectomy and hysterectomy had been done.

Upper midline incision. Freeing of gall bladder adhesions, mobilization of the ligament of Treitz by transverse incision of the contracted band, which completely relieved the angulation and allowed the previously distended duodenum immediately to collapse. 100 cc. of "amphetin" were instilled and routine closure of the belly wall without drainage.

**Preoperative Diagnosis:** Partial duodenal occlusion due to shortened Ligament of Treitz.

**Postoperative Diagnosis:** Marked omental and intestinal adhesions and short fibrous Ligament of Treitz.

## Continuation of Progress Record:

May 17, 1934: Laparotomy done and adhesions freed, postoperative condition satisfactory.—Dr. Byers.

May 19, 1934: Even convalescence, bowels open, no vomiting.—Dr. Evers.

May 21, 1934: Nothing unusual, appetite good, no vomiting.—Dr. Evers.

May 24, 1934: Stitches out, wound clean, uneventful postoperative course.—Dr. Evers.

May 26, 1934: Discharged.—Dr. Evers.

**Condition of discharge:** Recovered, cured.—Dr. Evers. Feb. 8, 1935: I received a letter from the patient in which she writes as follows: "I am very well and am more regular than I have ever been in my life, can eat practically anything, seldom have indigestion and no nausea that I used to have after every meal."

## SUMMARY

A case of incomplete intestinal obstruction due to shortening of ligament of Treitz has been presented because of the rather uncommon nature of the obstruction, and to show the value of close fluoroscopic observation. This case was completely missed in a previous gastro-intestinal series elsewhere.

# SECTION I—Clinical Medicine: Diseases of Digestion

## Intestinal Tuberculosis

### A Clinical, Roentgenological and Pathological Study of 2086 Patients Affected With Pulmonary Tuberculosis

By

EMIL GRANET, A.B., M.D.\*  
NEW YORK CITY, NEW YORK

ULCERATIVE intestinal tuberculosis is a common disease. That it must be so regarded is shown by the following: 72% of our fatal cases of pulmonary tuberculosis at the Metropolitan Hospital were found at autopsy to have ulcerative enteritis. Furthermore, recent reliable post mortem studies from various localities report ulcerative enteritis as a complication of pulmonary tuberculosis in 65-90%. The total morbidity from pulmonary tuberculosis cannot be estimated accurately. However, vital statistics for New York City in 1933 place the total deaths from pulmonary tuberculosis at 4,500. Based on the statistics quoted, a conservative assumption is that 65% or 3,000 of these suffered with ulcerative enteritis for some time before death. It is apparent from this that ulcerative enteritis is a frequent complication of pulmonary tuberculosis and as such must be seriously regarded as a common clinical entity.

Tuberculous enteritis assumes major importance when present in a patient because of its profound effect on the course of the pulmonary disease. It gravely influences the treatment and prognosis of the patient. We know that a prime factor in treating a tuberculous patient is maintaining or restoring nutrition. The presence of an ulcerative enteritis, interfering as it does with the assimilation of food and furthering the absorption of intestinal toxins, minimizes the possibility of maintaining the nutrition of the patient. Certain it is that without this complication many tuberculous patients now doomed would go on to a successful recovery.

Undoubtedly the presence of extensive intestinal ulcerative lesions at the time of diagnosis accounts for the relatively poor therapeutic results. Brown and Sampson (1), Gram and Flemming-Møller (2), and Klein (3) have had encouraging results only in individual cases. It is reasonable to assume, therefore, that with early diagnosis in the stage of minimal ulceration, the curability of intestinal tuberculosis would be greatly enhanced. With this aim in view this study was instituted. Important factors contributing to

TABLE I

*Relative Incidence of Gastro-Intestinal Symptoms in 1743 Patients Examined Roentgenologically for Tuberculous Enteritis.*

| Class                             | Positive With Enteritis | Negative No Enteritis | Total Patients |
|-----------------------------------|-------------------------|-----------------------|----------------|
| G. I. Symptoms Absent             | 527                     | 824                   | 1351           |
| G. I. Symptoms Present            | 217                     | 175                   | 392            |
| G. I. Symptoms Absent in Percent  | 71.0%                   | 82.5%                 | 77.5%          |
| G. I. Symptoms Present in Percent | 29.0%                   | 17.5%                 | 22.5%          |
| All Patients                      | 100%                    | 100%                  | 100%           |

ward a practical method of early diagnosis of tuberculous enteritis have been investigated and evaluated.

Since 1919, when Brown and Sampson published their comprehensive monograph on this subject, many clinical studies have been reported: Smithies *et al.*, (4), Williams (5), Lemon (6). In reviewing these papers one is impressed by the great variety of clinical material, the lack of uniformity of clinical factors and methods of study, and consequently, the wide disparity of statistical data. In this work I have attempted to parallel the method of study used by Brown and Sampson and their associates so far as was practicable with the clinical material and facilities at the Metropolitan Hospital in New York City.

Brown and Sampson report a positive clinical diagnosis of ulcerative enteritis in 1465 (26.4%) of 5542 tuberculous patients from Trudeau and Saranac Lake.

Klein (3) made a clinical diagnosis of tuberculous enteritis in 187 (17%) of 1078 patients with pulmonary tuberculosis in the Veteran's Bureau Hospital at Sunmount.

Williams (4), also at Sunmount, investigated 1088 tuberculous patients. 206 (19%) were considered to have intestinal tuberculosis, distributed according to the type of pulmonary tuberculosis present as follows:

Of 62 minimal cases, 1 had intestinal tuberculosis.

Of 273 moderately advanced cases, 15 (6%) had intestinal tuberculosis.

Of 753 far advanced cases 190 (26%) had intestinal tuberculosis.

\*Associate Attending Physician, Metropolitan Hospital; Asst. Radiographer, Gouverneur Hospital; Instructor in Post-Graduate Medicine, Columbia University.  
Submitted March 7, 1935.

## MATERIAL

2086 patients with pulmonary tuberculosis were personally examined by me for the presence of intestinal tuberculosis. Many of these were re-examined so that the total number of examinations was 2416. These patients were consecutive admissions with the exception that far-advanced toxic, or terminal cases were excluded from this study. Minimal cases as a rule are not admitted to this hospital. Of the 2086 patients, 800 (38%) were found to have definite radiographic evidence of tuberculous enteritis; 1286 (62%) were negative. Patients in whom a doubtful or suspicious diagnosis of enteritis was made and in whom re-examination could not be performed were included in the negative group.

The following factors were considered significant in explaining our comparatively high figures. These patients were largely indigent. For this reason, previous to admission many had had inadequate medical care, many were undernourished and improperly fed and a number were chronic alcoholics. A large number had engaged in manual labor despite the presence of a tuberculous toxemia. Many were Nordics, Orientals and Negroes, racial types known to have little immunity to tuberculosis. Hygienic measures were neglected; many patients persisted in swallowing their sputum. Foci of infection in the teeth, tonsils and prostate were common. Minimal tuberculosis was exceptional; in most of the group the primary lesion was classified as moderately advanced or far advanced.

## METHOD OF STUDY

## 1. Roentgenoscopic.

Patients were examined fluoroscopically 7-8 hours after barium was administered orally following an overnight fast. Films were taken infrequently as this was deemed expensive and unnecessary in the majority of cases. In those patients where doubt existed in the interpretation of findings, re-examination was performed after an interval of at least one week. Persistently doubtful cases were classified as negative. Colon examination by barium enema was performed only exceptionally to help clarify a doubtful diagnosis.

A roentgenographic diagnosis of ulcerative enteritis was considered justified if one or more of the following signs was present:

TABLE II

*Analysis of 392 Pulmonary Tuberculosis Patients with Gastro-Intestinal Symptoms*

| Symptoms             | Patients With      |                       | Symptoms           |                       |
|----------------------|--------------------|-----------------------|--------------------|-----------------------|
|                      | Positive Enteritis | Negative No Enteritis | Positive Enteritis | Negative No Enteritis |
| Total                | 217                | 175                   | 100%               | 100%                  |
| Pain                 | 110                | 73                    | 50                 | 41.0                  |
| Spasmodic            | 44                 | 58                    | 20                 | 33.0                  |
| Generalized          | 47                 | 26                    | 22                 | 16.0                  |
| Right Lower Quadrant | 22                 | 9                     | 10                 | 5.0                   |
| Diarrhea             | 55                 | 30                    | 25.0               | 17.0                  |
| Constipation         | 31                 | 41                    | 14.5               | 21.0                  |
| Dyspepsia            |                    |                       |                    |                       |
| Bloating             | 40                 | 33                    | 18.5               | 19.0                  |
| Belching             |                    |                       |                    |                       |
| Vomiting             | 8                  | 10                    | 3.6                | 5.5                   |
| Constipation         |                    |                       |                    |                       |
| Alternating Diarrhea | 11                 | 7                     | 5.0                | 4.0                   |

## A. Cecum and Ascending Colon.

1. Stierlin phenomenon.
2. Spasitic filling defect.

3. Filling defect with palpable tumor (granuloma).
4. Persistent irregularity of cecum after re-examination.
  - a. Non-filling.
  - b. Narrowing.
  - c. Persistent irregular spasm of ceco-colic valve.
5. Persistent mottling after re-examination.

## B. Ileum.

1. Segmentation and dilation of ileal loops.
2. Matted, adherent ileal loops.

Presumptive signs such as ileal stasis, hypermotility in the colon, gastric residue and ileo-cecal tenderness when present alone were deemed insufficient evidence on which to base a positive diagnosis.

We did not attempt to interpret lesions in the transverse and descending colon with barium meal administered orally. Several patients when first examined had normal colons. After several weeks or months, re-examination revealed signs of ulcerative enteritis. The contrary was true in other patients in whom the original defect disappeared and an increasingly normal picture ensued. The latter were considered cured or markedly improved.

A discussion of roentgen ray findings and their interpretation is beyond the scope of this paper. The present status of our knowledge of this phase of diagnosis is ably discussed by Brown and Sampson (1), Cherry (6), Gershon-Cohen (7), Gram and Flemming-Moller (2). Extreme conservatism and care are necessary to properly interpret defects in the contour of the ileum and proximal colon. Dr. Gosta Forsell, the eminent radiographer, emphasizes this in his discussion of Gram and Flemming-Moller's paper. He stresses the fact that even in normal individuals "the plastic movements of the mucous membrane can cause the form of the lumen to change from an even tube to the most varied formations. The mucosa may fill it entirely in such a manner that the roentgen picture shows a complete defect or in such a manner that the lumen becomes of varying width and shapes. Such an authoritative statement emphasizes the importance of careful, prolonged fluoroscopic observation and frequent re-examination of doubtful cases to definitely establish the organic origin of a roentgen defect.

The accuracy of diagnosis is difficult to check in most cases. Few patients are operated on and in those that come to autopsy there is often a lapse of months between the time of roentgen examination and the death of the patient. Intestinal lesions may develop rapidly in this terminal stage. Careful roentgenographic diagnosis can be accurate, however, as is shown by the following figures: Brown and Sampson diagnosed tuberculous enteritis clinically in 92 patients who later were operated on or came to post-mortem. In only three were lesions absent in the colon at autopsy. A normal intestine had been diagnosed by X-Ray in 88 patients who were later operated on or autopsied. Only one of them showed ulcerative colitis.

Our results also show a relatively high degree of diagnostic accuracy. Autopsies were performed on 59 of our patients who previously had been examined roentgenographically for the presence of intestinal tuberculosis. In 43 of these, X-Ray diagnosis was confirmed, 29 were positive for enteritis; and in 14, negative X-Ray findings were confirmed by the absence of intestinal lesions. In 6 patients diagnosed roentgenoscopically normal, intestinal ulceration was shown at autopsy. 10 patients, in whom a negative diagnosis

TABLE III

*Analysis of Sputum of 1719 Patients Examined Roentgenographically for the Presence of Tuberculous Enteritis*

| Class    | Number             |                       | Percent            |                       |
|----------|--------------------|-----------------------|--------------------|-----------------------|
|          | Positive Enteritis | Negative No Enteritis | Positive Enteritis | Negative No Enteritis |
| Total    | 740                | 979                   | 100%               | 100%                  |
| Sputum   |                    |                       |                    |                       |
| Positive | 548                | 550                   | 74.0%              | 56.0%                 |
| Negative | 34                 | 180                   | 4.5%               | 18.3%                 |
| Doubtful | 158                | 249                   | 21.3%              | 25.4%                 |

had been made clinically, revealed ulcerative enteritis at autopsy. However, in this last group of 10, the interval between X-Ray examination and autopsy varied from 6 to 28 months. It is probable that intestinal ulcers had developed in the interim, and for this reason the validity of these cases should be questioned. Thus, excluding the 10 cases with the long time interval between examination, X-Ray diagnosis was correct in 43 (88%) of 49 patients in this group.

### 2. Symptoms.

Disease entities associated with toxemia or metabolic disturbances frequently manifest themselves in gastro-intestinal symptoms; this is true also of tuberculosis. It is often difficult, therefore, in a tuberculous individual to differentiate between the gastro-intestinal symptoms caused presumably by the absorption of toxins from the pulmonary lesions, and symptoms engendered directly by the ulcerative enteritis. For this reason, in order to simplify this study, constitutional symptoms such as anorexia, loss of weight, weakness, nervousness, fever; and objective symptoms, such as local tenderness, distention and mass formation were excluded. Only gastro-intestinal symptoms which could be attributed directly to the intestinal pathology were included. Patients were questioned for the presence of symptoms at the time of X-Ray examination. Common complaints such as dyspepsia and constipation were recorded only when the onset of these symptoms approximated the date of onset of pulmonary symptomatology. Vomiting following prolonged seizures of coughing was excluded as a primary gastro-intestinal symptom, as were transient attacks of diarrhea following dietary indiscretions.

We have progressed greatly from the day when intestinal tuberculosis was diagnosed by the onset of intractable diarrhea. All observers agree that symptoms often occur late in tuberculous enteritis. Of 76 patients with tuberculous enteritis who came to post-mortem, Walsh (9) reported that 34% had no gastro-intestinal symptoms during life. I was amazed by the complete absence of gastro-intestinal symptoms in many of our patients who showed roentgen signs of extensive intestinal ulceration. Our figures show that, of 744 tuberculous patients with definite roentgenographic evidence of ulcerative enteritis, only 217 (29%) complained of gastro-intestinal symptoms at the time of examination. 527 (71%) of these had no intestinal symptoms. In 999 tuberculous patients in whom roentgenography showed a relatively normal gastro-intestinal tract 175 (18%) complained of gastro-intestinal symptoms. (Tables I and II).

A number of our positive enteritis cases who were

symptom-free at the time of roentgen examination later developed gastro-intestinal symptoms. In others of this group, symptomatic periods alternated with symptom-free periods. A small number of enteritis patients with symptoms at the time of examination gradually became symptom-free. This change generally coincided with improvement in the original roentgen defect.

It seemed extremely important to us that only 29% of our enteritis cases complained of gastro-intestinal symptoms as compared with 18% of symptomatic cases in the roentgenographically normal group. The etiology of symptoms in this latter group is conjectural at this time and is to be investigated in another study. The comparatively small percentage of symptomatic patients in our positive enteritis group requires elucidation. Many of our patients by their poverty become inured to the rigors of life and consequently are largely hyposensitive to physical discomfort. They tend to minimize the significance of dyspepsia and mild abdominal pain and consequently fail to report these symptoms. The order of frequency of symptoms for patients with intestinal tuberculosis in this group was as follows (Table II): pain, diarrhea, dyspepsia, constipation, constipation alternating with diarrhea, vomiting. In patients with a roentgenographically normal intestine the frequency in order of occurrence was: pain, constipation, dyspepsia, diarrhea, vomiting and constipation alternating with diarrhea. The remarkably small percentage of patients with gastro-intestinal symptoms in our enteritis group emphasizes strikingly the futility of depending on symptomatology to aid in the early diagnosis of intestinal tuberculosis.

### 3. Sputum.

Investigators are largely agreed that tuberculous enteritis occurs as a secondary complication of pulmonary tuberculosis. Extension of the disease to the intestines takes place by direct contamination of the intestinal tract with tubercle bacilli swallowed in the sputum. Hence we expect patients with tuberculous enteritis to have or to have had positive sputums. Furthermore, it follows that a patient with consistently negative sputum reports is unlikely to acquire tuberculous enteritis. This direct relationship of positive sputum to intestinal tuberculosis is important from a diagnostic and prognostic standpoint; consequently it was investigated as part of this study.

The presence or absence of tubercle bacilli in the sputum of patients in this series was noted at the time of intestinal radiography. To simplify essential factors, the method of recording was arbitrarily fixed as follows: Positive—if tubercle bacilli were found at any time during the case history in either sputum or gastric lavage returns. Negative—if tubercle bacilli were consistently absent in five or more concentrated sputum examinations or absent in the gastric lavage returns. Doubtful—if less than five examinations with negative findings were performed up to the time of X-ray examination. Ulmar and Ornstein (10) have frequently demonstrated tubercle bacilli in the gastric lavage returns of patients with consistently negative sputum. Diagnostic lavage of patients with negative sputa has been made a routine practice on this service.

Our investigation confirmed the direct relationship between positive sputum and intestinal tuberculosis. Of 740 patients with intestinal tuberculosis the spu-

tum was negative for tubercle bacilli in only 34 (4.5%). On the other hand of 979 patients with a roentgenographically normal intestinal tract, negative sputum was found in 180 (18.3%). (Table III). Our figures approximate those of Brown and Sampson who report 55 patients (11%) with negative sputum in a group of 519 cases of secondary tuberculous enteritis. From these findings we believe, therefore, that the presence of tubercle bacilli in the sputum favors the onset of a secondary intestinal tuberculosis and further, that a consistently negative sputum precludes this complication. Patients with positive sputum continually re-infect the intestinal mucous membrane by swallowing tubercle-laden sputa. In these patients, therefore, whenever possible, pneumothorax or thoracoplasty is instituted early in an attempt to rid the sputum of tubercle bacilli. Where this desideratum has been attained, healing of existing intestinal lesions without the danger of further infection becomes possible. In a small number of our patients now under observation, clinical and roentgenographic improvement in the enteritis picture followed pulmonary surgical procedures.

#### 4. Sigmoidoscopy.

Peri-anal tuberculosis is frequently seen. Walsh (8) reported 9% in 100 autopsies on patients with pulmonary tuberculosis. Martin (10) found tuberculous ulcers in 5 of 20 patients with far advanced intestinal tuberculosis examined proctoscopically. The rectum was involved in 16% of patients with intestinal tuberculosis examined at post mortem by Goldberg, Sweany and Brown (11).

150 consecutive patients in our series were sigmoidoscoped. Bedridden, toxic patients were excluded. Two patients only in this series showed discrete ulcers in the rectum which had the clinical appearance of tuberculous ulcers. Biopsy was not performed. It seems fair to conclude from this that ulcerative proctitis is a complication which develops late in the disease and sigmoidoscopy, therefore, as an early diagnostic measure is of little value.

Examination of the gastric chemistry, the feces and physical examination, except in tuberculous peritonitis and granuloma of the cecum gave little evidence of practical diagnostic value, and consequently were not considered in this study.

### POST MORTEM STUDIES

#### A. Pulmonary Lesions.

The post mortem study of secondary tuberculous enteritis brings out many facts and relationships which are of use in the clinical diagnosis of this condition. Especially so is the relationship of the pulmonary lesion to the secondary lesion in the intestines. The presence of cavitation in the lungs of a tuberculous patient usually is associated with the presence of positive tubercle bacilli in the sputum of that individual. It has been shown that positive sputum predicates ulcerative enteritis in many cases. We, therefore, expect to find pulmonary cavities in most patients with tuberculous enteritis. This direct relationship has been demonstrated by Brown and Sampson (1) in clinical studies. They showed that in 519 patients with intestinal tuberculosis diagnosed roentgenographically, 329 (63%) had pulmonary cavities. Klein (2) found pulmonary cavities in 214 of 233 cases of secondary intestinal tuberculosis.

In our patients, post mortem examinations confirmed

TABLE IV

*Pulmonary Antra and Tuberculous Enteritis in 266 Autopsied Pulmonary Tuberculosis Patients*

|                | Number               |                    | Percent              |                    |
|----------------|----------------------|--------------------|----------------------|--------------------|
|                | Ulcerative Enteritis | Normal G. I. Tract | Ulcerative Enteritis | Normal G. I. Tract |
| Total          | 192                  | 74                 | 100%                 | 100%               |
| Cavity Present | 185                  | 45                 | 95.4%                | 61.0%              |
| Cavity Absent  | 7                    | 29                 | 3.6%                 | 39.0%              |

the direct relationship between pulmonary cavitation and ulcerative enteritis. (Table IV). Secondary ulcerative enteritis was present in 192 (72%) of 266 patients dead of pulmonary tuberculosis. 185 (95.4%) of the 192 enteritis cases had cavities in the lungs and only 7 (3.6%) had no open lung lesions. The converse of this does not follow. Thus, of the 74 patients in this group who were negative for ulcerative enteritis, 45 had pulmonary cavities and in 29 the lung had no open lesions. The clinical inference to be drawn from these figures is that in tuberculous patients with pulmonary cavity, the gastro-intestinal tract is very likely to become the seat of a secondary ulcerative enteritis. Hence, these patients should be investigated with the possibility of this diagnosis in view.

#### B. Distribution of Intestinal Lesions.

Observers are generally agreed that 80% of intestinal tuberculosis occurs in part at the ileo-cecal region. The explanation for this distribution lies in the anatomical and physiological factors which favor the local implantation of the tubercle bacillus. Among these may be mentioned concentration of lymphatic tissue (Peyer's patches and solitary follicles) in the ileo-cecal region, the presence here of fluid intestinal chyme, stasis of the intestinal contents in the cecum and at the ileo-cecal valve, the mechanical irritation of the stream of chyme against the edges of the ileo-cecal valve and the point in the cecum on which this stream impinges.

The localization of the intestinal lesions in the ileo-cecal region has an important clinical significance in roentgenographic diagnosis. As stated above, most positive diagnoses of tuberculous enteritis follow the roentgenoscopic finding of defects in contour of the barium filled cecum and ascending colon.

In our series of 192 patients with tuberculous enteritis, the cecal region was the seat of pathology, wholly or in part, in 167 (86%). The distribution of lesions in this group was tabulated according to the anatomical location in individual cases. (Table V). Localization in the ileo-cecal region was most frequent (53), involvement of the entire tract was next (38), cecum alone was third (33). From a study of the distribution of the lesions we can infer that about 90% of the intestinal lesions occur in the terminal ileum, cecum and ascending colon. In this portion of the gastro-intestinal tract, ulcerative lesions usually manifest themselves as spastic defects in contour and so are recognizable on roentgenographic examination. We have no reliable method of recognizing early lesions in the jejunum and proximal ileum, but we find that lesions in this region occur in only 14% of our



TABLE V

*Distribution of Lesions in 192 Cases of Tuberculous Enteritis*

| Location                                   | Number | Percent |
|--------------------------------------------|--------|---------|
| Total                                      | 192    | 100%    |
| Ileo-Cecal                                 | 53     | 31.0%   |
| Cecum Only                                 | 33     | 17.0%   |
| Entire Small and Large Intestine           | 38     | 19.0%   |
| Ileum, Cecum and Ascending Colon           | 27     | 14.0%   |
| Ileum Only                                 | 19     | 10.0%   |
| Cecum, Ascending Colon                     | 9      | 4.5%    |
| Jejunum Only                               | 3      | 1.7%    |
| Jejunum, Ileum, Cecum                      | 4      | 2.0%    |
| Jejunum, Cecum                             | 1      | 0.5%    |
| Jejunum, Ileum                             | 3      | 1.7%    |
| Ascending, Transverse and Descending Colon | 1      | 0.5%    |
| Sigmoid Only                               | 1      | 0.5%    |

autopsied cases. During life it is likely that the number of cases with jejunal ulcerations must be even smaller and, therefore, the diagnostic error here encountered can be disregarded with impunity.

#### DIFFERENTIAL DIAGNOSIS

Pathological conditions, non-tuberculous in origin, occurring in the terminal ileum or colon of patients with pulmonary tuberculosis are likely to be inaccurately diagnosed as tuberculous. This is so because of the morphological similarity of roentgen defects in this region. Suffice it, in this report, merely to mention several important intestinal lesions that require differentiation.

*Terminal ileitis*, a non-specific inflammatory lesion involving the terminal ileum, recently described by Crohn *et al.*, (12) may simulate a spastic narrowed tuberculous *ileitis*. Malignant neoplasms of the cecum cannot be differentiated roentgenographically from tuberculous granuloma of the cecum. *Inflammatory diverticulitis* of the colon occurring in the cecum and ascending colon may stimulate tuberculous enteritis. In these conditions only exploratory laparotomy can establish the correct diagnosis and should always be performed early in doubtful cases.

*Chronic non-specific ulcerative colitis and amebic or bacillary dysentery* when localized, can closely resemble the roentgen picture of tuberculous enteritis. In these conditions diagnosis depends on the clinical course of the case, sigmoidoscopy, the bacteriology and serology of the stool cultures, stool examinations for ameba, and the successful response to specific therapy when this is feasible.

On our service we have made it a practical rule that, in tuberculosis patients, intestinal lesions showing persistent roentgen defects are considered tuberculous until proved otherwise, especially when the sputum is positive for tubercle bacilli.

#### THERAPY

The successful treatment of intestinal tuberculosis depends primarily on one key factor, namely, inactivation of the source of infection in the lungs. Absorption of toxins from active lung lesions by their noxious systemic effect prevents healing of intestinal lesions. Furthermore, the intestinal mucosa is constantly being re-infected with tubercle bacilli swallowed in the sputum expectorated from active parenchymal foci. While these factors are present it is useless to expect permanent cure in the secondary intestinal lesions. As stated above, the prime emphasis in therapy must be directed toward attaining a negative sputum and a decrease in toxic absorption.

The treatment of the intestinal lesions must be undertaken simultaneously and the measures used are twofold, *general and specific*. The general measures undertake to improve nutrition, help tissue repair, and strengthen immunity. These include actino-therapy, a high caloric, low roughage diet, the administration of vitamins C and D, iron for secondary anemia, calcium salts, and where indicated, insulin to stimulate appetite.

Specific local treatment is directed primarily toward fostering peristaltic rest in the involved segments of the intestine. Treatment depends on individual symptomatology and must be changed frequently to suit the clinical course of the case. A smooth, low residue, high caloric diet, similar to a maintenance peptic ulcer diet, to which is added tomato juice and cod liver oil as advocated by McConkey, is our standard dietary. Such a diet reduces peristaltic action to a minimum and provides an excess of vitamins C and D, shown to be of value in the metabolizing of calcium and the stimulation of mucosal healing. Abdominal pain is controlled by heat or adequate sedatives. Constipation is helped by small amounts of mineral oil or by gently administered warm saline enemas. Diarrhea is controlled by administration of barium sulphate or kaolin in half ounce doses administered frequently and, if necessary, tincture opii deodorata in effective doses. Dyspeptic symptoms usually improve on sedation, carminatives or alkalies.

Surgical therapy has definite indications in the treatment of certain types of intestinal tuberculosis. Unfortunately it is often too long delayed. Granulomatous lesions should be resected. Acute tuberculous appendicitis is frequently seen and here operative delay may be costly. Perforation of tuberculous ulcers with resulting peritonitis is a condition always to be expected, and here neglect of immediate operative repair is fatal. Partial colectomy for early, localized, ulcerative tuberculosis has been advocated but we have not felt it an advisable procedure in our cases. Our experience has been that, with elimination of re-infection and careful individualization of symptomatic medical treatment as described, ulcerative intestinal lesions tend to improve clinically and roentgenographically. We have never observed consistent improvement in the intestinal lesions of patients in whose lungs the disease process increased in activity.

## SUMMARY AND CONCLUSION

Tuberculous enteritis is a common disease and is present in most patients with advanced pulmonary tuberculosis. 2086 tuberculous patients were studied clinically and pathologically in an attempt to delimit criteria which would facilitate early diagnosis and better therapeutic results. This study was limited to moderately advanced and advanced non-toxic patients with pulmonary tuberculosis.

Roentgenoscopy of the gastro-intestinal tract revealed lesions in 37% of our patients. Postmortem check-up showed a relatively high degree of accuracy for this method of diagnosis. A history of gastro-intestinal symptoms was found to be unreliable as a

diagnostic aid inasmuch as symptoms were absent in the majority of positive enteritis cases. Furthermore, the percentage of patients complaining of gastro-intestinal symptoms was only slightly greater in the positive enteritis group than in the negative patients. A study of the sputum showed tubercle bacilli in practically all positive enteritis cases. Similarly almost all fatal cases with enteritis had pulmonary cavities when examined at autopsy. Sigmoidoscopy revealed rectal involvement only in 2 of 150 patients examined.

Differential diagnosis was considered and principles of therapy were outlined.

Therapy was described briefly and emphasis was placed on treatment of the primary focus of infection as well as of the intestinal lesions.

## REFERENCES

1. Brown, L., and Sampson, H. L.: Intestinal Tuberculosis. Ed. 2. Phil. Lea and Febiger, 1930.
2. Gram, H. C., and Flemming-Moller, P.: Results of carbon arc light treatment of intestinal tuberculosis. *Acta Radiol.*, 11, 133-165, 1930.
3. Klein, L. B.: Quoted by Brown & Sampson.
4. Smithies, F., Weisman, and Fremmel, F.: Tuberculous enterocolitis. *J. A. M. A.*, 91, 1952-1959, 1928.
5. William, H. B.: Roentgenological diagnosis of intestinal tuberculosis. *U. S. Vet. Bur. Med. Bull.*, 6, 113-117, 1930.
6. Lemon, W. S.: Intestinal tuberculosis. III. Clinical studies relating to diagnosis. *Trans. Nat. Tuberc. Assn.*, 21, 186-199, 1925.
7. Cherry, H. H.: Signs of tuberculous enterocolitis. *Am. J. Roent. and Rad. Ther.*, 27, 65-82, 1932.
8. Gershor-Cohen, J.: Diagnosis of early ileocecal tuberculosis. Prelim. report with special reference to double contrast enema. *Am. J. Roent. and Rad. Ther.*, 21, 66, 367-388, 1930.
9. Walsh, J.: Statistics of autopsies on 100 cases dying of tuberculosis. *Trans. Nat. Tuberc. Assn.*, 5, 217, 1909.
10. Uman, D., and Ornstein, G. G.: Gastric examination in pulmonary tuberculosis with negative sputum; diagnostic importance. *J. A. M. A.*, 101, 835-838, 1933.
11. Martin, C. L.: Ulcers of the rectum and sigmoid. *J. A. M. A.*, 98, 27, 1932.
12. Goldberg, B.; Sweany, H. C., and Brown, R.: Pathological studies on tuberculous enteritis. *Am. Rev. Tuberc.*, 18, 744-766, Dec., 1928.
13. Crohn, B. B.; Ginsberg, L., and Oppenheimer, G. D.: Regional ileitis. *J. A. M. A.*, 99, 1323-29, Oct. 15, 1932.

## Stomach Lavage Microscopy as an Aid in the Diagnosis of Biliary Tract Disease\*

By

HENRY A. RAFSKY, M.D., F.A.C.P.<sup>†</sup>  
NEW YORK CITY, NEW YORK

(1)

IN a previous paper, I reported the fact that crystalline elements were observed in the stomach lavage of patients with cholelithiasis. In an effort to approximate the diagnostic significance of this finding, this subject was further investigated in a series of patients with and without biliary tract disease. In this study microphotographs of the crystalline elements seen in the stomach lavage, before operation, were compared with microphotographs of the crystals, found in the bile and stones removed from the gall bladder and bile ducts at the time of operation.

### MATERIAL

In this series 91 patients were studied and were grouped as follows:

1. 53 patients (58.2%) in whom biliary tract disease was diagnosed and who subsequently came to operation.
2. 18 patients (19.7%) in whom biliary tract disease was diagnosed but who did not come to operation.

3. 20 patients (22.1%) who comprised the control group. In these patients, there was no history or clinical evidence of biliary disease.

### METHOD OF STUDY

The method of procedure was as follows: A gastric lavage with warm tap water was performed in the morning, while the patient was in a fasting state. The lavage water was then collected and examined microscopically for crystalline elements. When crystals were present, they were usually found in the grayish or brownish red particles imbedded in the mucus or they were seen in the lavage water independently of the mucus. In the patients in groups 1 and 2, an attempt was made to do the gastric lavage in the morning, following an attack of biliary colic or gastric disturbances of sufficient severity to disturb the patient's sleep. It was found that when the lavage was obtained under these circumstances, the crystalline elements were present in large amounts.

In Group 1, there were fifty-three patients in whom biliary tract disease had been diagnosed and who subsequently came to operation. Crystalline elements were found in appreciable amounts in the stomach lavage, before operation, in forty-six of these patients (86.8%). In the remaining seven patients (13.2%) few or no crystals were seen in the gastric lavage. A study of the crystal morphology as observed in the

\*From The Einhorn Clinic, Medical and Surgical Divisions of The Lenox Hill Hospital; The Gastro-Enterological and Surgical Divisions of The Beth Israel Hospital, New York.  
<sup>†</sup>Associate Gastro-Enterologist, Beth Israel Hospital; Associate Gastro-Enterologist, Lenox Hill Hospital.  
Received January 17, 1935.

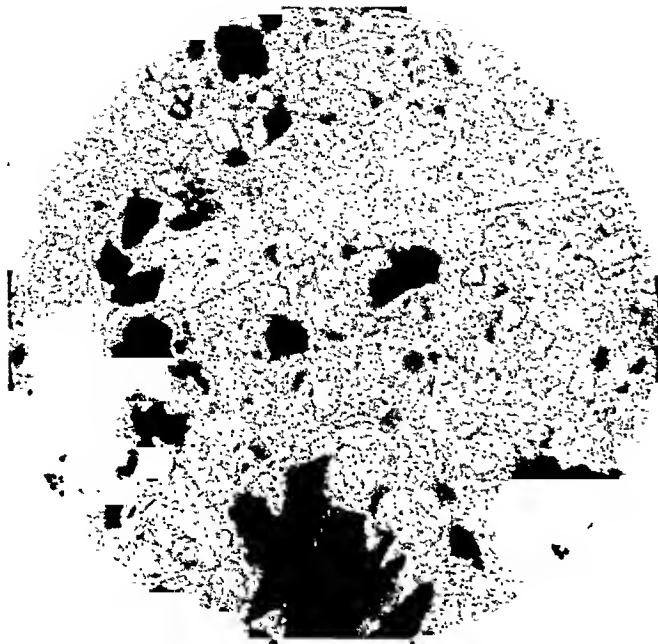


Fig. 1

stomach lavage, before operation, of the patients in this group, revealed the following: (Table 1.)

Numerous cholesterol crystals separately or together with carbonate crystals in seven patients (13.2%); a large amount of calcium bilirubinate pigment in five patients (9.4%); a shower of cholesterol crystals (with or without carbonate crystals) together with a moderate or large amount of calcium bilirubinate pigment in thirty-four patients (64.2%); and few or no crystalline elements in seven patients (13.2%). The operative findings of the patients in Group 1, were as follows: Calculous cholecystitis (including choledocholithiasis) in forty-one patients (77.3%); non-calculous cholecystitis in nine patients (16.9%); and no macroscopic evidence of biliary disease in three patients (5.8%).

Two of the patients in Group 1, had been subjected to cholecystectomy for gall stones, one, eleven years ago, and the other, nine years ago. An abundant amount of calcium bilirubinate pigment was found in the stomach lavage in both of these patients when they were examined recently. When they were operated again, stones were found in the common bile duct.

In Group 2, there were eighteen patients in whom biliary tract disease had been diagnosed, but who did not come to operation. Cholesterol and carbonate crystals and calcium bilirubinate pigment separately or collectively, were present in appreciable amounts in the stomach lavage in fifteen of these patients (83.3%). Few or no crystalline elements were found in three patients (16.7%). Cholecystography on the patients in this group revealed the following: Definite evidence of calculi or a persistent "no shadow" cholecystogram in five patients (27.8%); a gall bladder shadow fainter than normal in six patients (33.3%); roentgenographic evidence of a papilloma of the gall bladder in two patients (11.1%) and a normal func-

Fig. 1. Patient R. S.—Cholesterol and carbonate crystals together with calcium bilirubinate pigment (preoperative specimen of stomach lavage).

tioning gall bladder shadow in five patients (27.8%).

Group 3, which comprised the control group, consisted of twenty patients in whom there was no history or clinical evidence of biliary tract disease. Stomach lavage microscopy revealed the following: No crystalline elements in eleven patients (55.0%); few biliary crystals in seven patients (35.0%); numerous cholesterol crystals and a slight amount of calcium bilirubinate pigment in two patients (10.0%). One of the latter, when informed of the findings from the stomach lavage, recalled that he had a tape worm nine years ago. The other patient had diabetes.

# COMMENT

With a view of approximating the diagnostic significance of the presence of crystalline elements in the stomach lavage, a group of patients with and without biliary tract disease was studied. Cholesterol and carbonate crystals, as well as calcium bilirubinate pigment, separately or collectively, were found in most of the patients with proved calculous or non-calculous cholecystitis. In these patients with biliary tract disease, who came to operation, the crystalline elements observed in the preoperative specimen of stomach lavage were found to be similar to the crystals seen in stones and bile removed from the gall bladder, at operation. The crystals were found more consistently and in larger quantities when the lavage was performed in the morning following an attack of biliary colic.

The presence of the crystals in the stomach lavage is due to the regurgitation of the bile into the stomach. In about one-half of the patients the contents from the gastric lavage was deeply bile tinged.

Crystalline elements were found in the stomach lavage in patients with calculous as well as non-calculous cholecystitis. Of the patients in whom microscopic examination of the stomach lavage revealed many cholesterol crystals together with abundant calcium

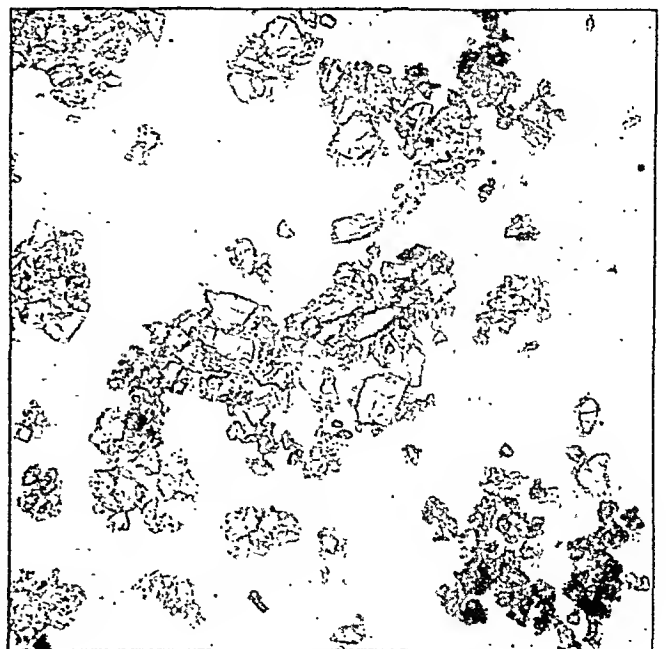


Fig. 2. Patient R. S.—Cholesterol and carbonate crystals together with calcium bilirubinate pigment (scrapping of stone).

Fig. 2



Fig. 3. Patient A. B.—Cholesterol crystals together with calcium bilirubinate pigment (preoperative specimen of stomach lavage).

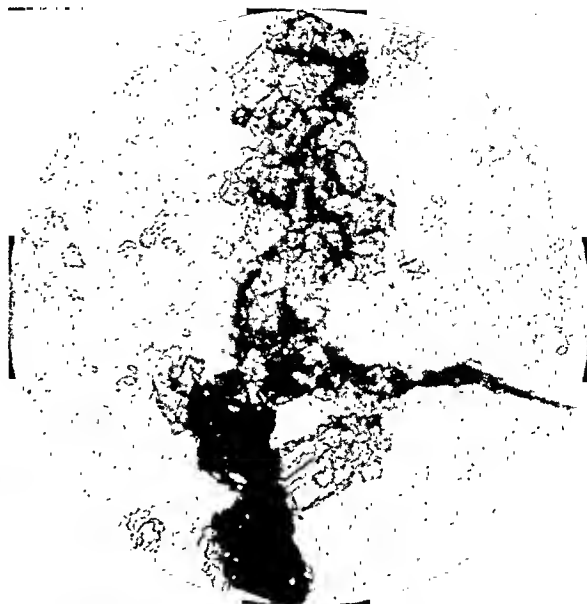


Fig. 4. Patient A. B.—Cholesterol crystals together with calcium bilirubinate pigment (scraping of stone).

bilirubinate pigment, cholelithiasis (including choledochlithiasis) was found in 97.1 per cent of the patients.

Crystalline elements, to have diagnostic significance, should be present in the stomach lavage in appreciable numbers. Few or no crystals in the stomach lavage,

nostic value of the microscopic examination of the stomach lavage in biliary tract disease:

#### CASE REPORTS

*Case 1.*—R. S., age 57, female, white, married, com-



Fig. 5. Patient J. K.—Cholesterol and carbonate crystals (preoperative specimen of stomach lavage).



Fig. 6. Patient J. K.—Cholesterol and carbonate crystals, bile stained mucus and slight amount of calcium bilirubinate pigment. (Bile from gall bladder).

however do not rule out biliary tract disease, especially if the examination is made when the patient is symptom free or if very large calculi are present in the gall bladder. More than one lavage may be necessary before the crystals are recovered.

The following case reports will illustrate the diag-

plained of periodic attacks of abdominal pain for five years. The pain was localized in the right upper quadrant, radiating to the right shoulder. Physical examination revealed tenderness over the gall bladder region. Microscopic examination of the stomach lavage showed the presence of cholesterol and carbonate crystals and calcium bilirubinate pigment in the same particle (Figure

1). Cholecystography indicated the presence of numerous biliary calculi. The patient was operated upon and about three hundred stones were removed from the gall bladder. The scrapings of one of these stones showed the presence of cholesterol and carbonate crystals and calcium bilirubinate pigment similar to those in the stomach lavage before operation (Figure 2.)

Case 2.—A. B., age 50, female, white, married, gave a history of recurrent attacks of biliary colic for seven years. The pain was localized over the gall bladder region and it radiated to the region of the spine. There was tenderness over the epigastrium and gall bladder regions. Microscopic examination of the stomach lavage revealed cholesterol crystals together with calcium bilirubinate pigment (Figure 3). Cholecystography showed a gall bladder shadow faintly outlined, but, no stones were discernable. The patient was operated and eleven stones were found in the gall bladder. The scrapings of one of these stones showed the presence of cholesterol crystals and calcium bilirubinate pigment (Figure 4).

Case 3.—J. K., white, male, married, gave a history of having had severe attacks of pain in the abdomen occurring about once monthly for the past two years. The pain was located in the epigastrium and radiated to the right shoulder and then down the right inguinal region. Physical examination revealed tenderness over the right upper quadrant. Microscopic examination of the stomach lavage showed the presence of cholesterol and carbonate crystals (Figure 5). Roentgenographic examination of the kidneys did not reveal any abnormality. A roentgenographic examination of the gastro-intestinal tract showed a pylorospasm with no definite evidence of ulceration. Cholecystography indicated a normal functioning gall bladder shadow. An exploratory laparotomy was performed on the patient and the following was found: The gall bladder was covered with adhesions especially on the right lower surface. Part of the adhesions were attached to the anterior wall of the second portion of the duodenum. The stomach and duodenum did not show any evidence of ulceration or malignancy. The gall bladder was removed. Microscopic examination of the bile from the gall bladder showed the presence of cholesterol and carbonate crystals (Figure 6). The report of the pathological examination of the gall bladder was "Chronic Catarrhal Cholecystitis".

### CONCLUSION

1. In a group of patients with proved calculous and

non-calculous cholecystitis the microscopic examination of the stomach lavage revealed the presence of biliary crystals in appreciable amounts in a large percentage of the patients.

TABLE I  
Comparative Study of the Crystal Morphology and Operative Findings of the Patients in Group 1

| Number of Cases | Crystalline Morphology                                                                                                                      | Operative Findings                                                                                                                                                                                                 |                               |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| 7<br>(13.2%)    | Numerous cholesterol crystals separately or together with carbonate crystals                                                                | 4—Calculous cholecystitis<br>3—Non-calculous cholecystitis                                                                                                                                                         | (57.1%)<br>(42.9%)            |
| 5<br>(9.4%)     | Large amount of calcium bilirubinate pigment                                                                                                | 2—Cholelithiasis<br>2—Non-calculous cholecystitis<br>1—No macroscopic evidence of biliary tract disease                                                                                                            | (40.0%)<br>(40.0%)<br>(20.0%) |
| 34<br>(64.2%)   | Numerous cholesterol crystals (with or without carbonate crystals) together with a moderate or large amount of calcium bilirubinate pigment | 23—Calculous cholecystitis (including cholelithiasis)<br>1—Non-calculous cholecystitis                                                                                                                             | (97.1%)<br>(2.9%)             |
| 7<br>(13.2%)    | Few or no crystalline elements                                                                                                              | 2—Calculous cholecystitis (stones were very large)<br>3—Non-calculous cholecystitis (in one of these cases, a carcinoma of the cystic duct was also present)<br>2—No macroscopic evidence of biliary tract disease | (28.5%)<br>(43.0%)<br>(28.5%) |

2. Crystalline elements observed in the stomach lavage before operation were similar to those crystals seen in the bile and stones removed from the gall bladder at the time of operation.

3. In a group of patients without biliary tract disease, microscopic examination of the stomach lavage revealed few or no biliary crystals in a large percentage of the patients.

### REFERENCE

1. Rafsky, H. A.: Crystalline Elements in the Stomach Lavage of Patients with Cholelithiasis. *J. Lab. and Clin. Med.*, 19:959, June, 1934.

## A Clinical Interpretation of Duodenal Diverticulum\*

By

HERMAN H. RIECKER, M.D.†  
ANN ARBOR, MICHIGAN

**R**EGARDED as an anatomical curiosity until 1913, when the first case was diagnosed by Roentgen ray, the duodenal diverticulum, now not an uncommon lesion, still lacks uniformity in the interpretation of its etiology and significance in gastroenterology. Its classification has been most studiously attempted by Odgers (1), who, however, followed the pre-roentgen conception of a primary type (false, congenital, *hernias*

*tunicaries*), occurring in the second or third part of the duodenum, and the secondary type (true, acquired) appearing only in the first part of the duodenum. Odgers' views, reflecting those of the pathologist, are that the "primary" type probably is due to congenital areas of local, decreased resistance to pressure, and he believes, with Nagel (2), that it is not associated etiologically with ulcer.

Bensaude (3) suggested five predominant groups of symptoms referable to the presence of diverticula, but these are confusing and difficult to apply in attempting

\*From the Department of Internal Medicine, University of Michigan Medical School.

†Assistant Professor of Internal Medicine.  
Submitted April 3, 1935.



Fig. 1

a clinical diagnosis. Since gastro-intestinal symptoms almost always are caused by an abnormal motility there is some question as to whether duodenal pouching is the cause or result of motility changes in this organ. It is impossible consistently to diagnose a diverticulum from the history alone and even to hazard a guess as to its presence is not wise.

It was with the problem of defining a possible clinical picture and arriving at a clinical interpretation of the meaning of the diverticulum as revealed by X-ray that the 35 cases in the files of the University of Michigan Hospital were reviewed; many of these cases personally were examined. The following results came from this study:

Twenty-two (22) cases had the usual history of duodenal ulcer and were so diagnosed provisionally by the examining physician.

Thirteen (13) of these were cases of peptic ulcer associated with diverticulum. In the remainder no lesion of the stomach or duodenum was demonstrated other than diverticulum. Of these 13, the diverticulum was localized by X-ray in the first portion of the duodenum in three, in the second portion in five, and in the third portion in five.

This survey indicated in a surprising way that the most common history and the most consistent associated lesion was peptic ulcer.

A review of the literature since 1914 was made in an effort to confirm or deny three current statements that diverticulum is usually of congenital origin, has no definite clinical history, is a purely incidental finding, and is not associated commonly with peptic ulcer or other disease of the upper abdomen. In many clinical case-reports the data presented was insufficient to

Fig. 1. Showing ulcer and large diverticulum in third portion. Female *aet* 54.

be of value for this purpose. However, 40 cases were found in which peptic ulcer was associated with diverticulum; the location of the latter, where stated, is detailed in Table I.

My own cases, as well as those found in the literature, indicated definitely that duodenal ulcer not uncommonly preceded the appearance of the diverticulum. There was no particular site for the location of such diverticula, as would be postulated necessarily in the classification of Odgers' and others who believe that only the secondary type is associated with this lesion.

Clairmont (4) gave an excellent discussion of this factor, recognizing cases in which ulcer preceded diverticulum. Denis (5) wrote that, clinically, the diverticulum often gives the symptoms commonly attributed to ulcer. Spriggs and Marxer (6) believed that, as a rule, the diverticula are not congenital and not associated with ulcer, although they report 47 per cent of 38 cases having epigastric distress after meals. In 30 cases reported by Cole and Dudley (7) eleven had pylorospasm and three showed gastric ulcer. In 100 cases characterized usually by epigastric distress and pylorospasm, and diagnosed as unstable or irritable duodenum, Friedenwald (8) found five instances of duodenal pouching. Gibbon (9) reported 20 cases, in nine of which epigastric symptoms occurred one to four hours after meals. Edwards (10) classified the symptomatology of 27 cases into (1) the flatulent dyspepsia of a filled pouch, and (2) epigastric pains after food which he interpreted as diverticulitis. Spriggs (11) in reporting 10 cases says that the diverticulum usually does not cause symptoms although in nine of these there was other abdominal disease. Sennett (12) reported four cases, one of which was associated with ulcer and the other presenting epigastric symptoms



Fig. 2

Fig. 2. Ulcer of duodenum. Diverticulum not visible as such but showing what appears to be a pouch in first portion of duodenum.



similar to those of ulcer. Zanetti (13), in discussing ulcer and ulcerated diverticulum, says that in his experience there is no difference between the symptom of ulcer of the bulb and of lesions further along in the duodenum, suggesting a belief that a diverticulitis can cause the symptoms of ulcer. Smithies, in discussing a paper by Case in 1920 (14), said that the symptomatology (of diverticulum alone) does not resemble that of ulcer. Kellogg (15), in discussing the symptoms, says that the pain frequently is intermittent, usually related to the taking of food and occurring from one to three hours after eating.

The usual duodenal ulcer history is closely simulated by reflex pylorospasm, by duodenitis, and by the irritable duodenum described by Friedenwald, and a diverticulum, of course, can be found under such circumstances. It is doubtful whether a diverticulum ever is primary or congenital, although a congenital predisposition for such lesion easily can be postulated. In one of our cases in whom an operation was preferred healed ulcer was found in a diverticulum of the first portion, but as a rule the pouch in this location is opposite the ulcer.

In 1893, Dr. Charlewood Turner was quoted by Perry and Shaw (16) as follows: "The pouching of the wall of the duodenum is to be attributed to a distension from irregular and spastic contraction due to irritation of the ulcerated surfaces." This gem of clinical reasoning appears to be the soundest explanation of origin of diverticula because the pouching occurs at the site of entering veins along the attachment of the duodenum usually in older subjects, and very rarely in children.

That a reflex spasm of the duodenum may be postulated to explain those cases in which an ulcer could not have been present is shown by the frequency of disease in other parts of the gastro-intestinal system in reported cases. In one of our cases there was a

cancer of the colon and in several, gallstones. In several case reports gallstones were found either by X-ray or at operation. A local spasm of the pyloric area usually accompanies active ulcer and the large majority of diverticula are of the false or herniated type, thus offering a sound functional basis for their formation. Lensmayer and Baldwin's (17) 60 post mortem examinations showed only four true types, all in the first part of the duodenum.

In two of our cases the diverticulum from a series of X-ray studies appeared to have developed several years after the ulcer had been demonstrated. Fig. 1 illustrates such a case in a woman 54 years of age in whom ulcer had been present periodically for 30 years. This diverticulum was not found in studies five years previously. It is obvious from the cases reported that there is neither a relation between the symptoms and the site of the diverticulum, nor between the presence of an ulcer and the position of the diverticulum. The evidence from a clinical standpoint does not permit a classification such as that of Odgers'. A queer event occurred in one of our cases in which a man of 44 years complained of symptoms strongly suggestive of ulcer over a period of 15 years, his father having died of cancer of the stomach. The X-ray diagnosis was duodenal diverticulum. A second X-ray study 10 years later failed to demonstrate the diverticulum. This instance, together with the fact that surgeons complain commonly of not being able to find a roentgen-demonstrated diverticulum (but sometimes an ulcer), brings into question the actual incidence not only of the deformity but associated ulcer as well, since the latter heals and reappears periodically in a lifetime. Because of the difficulty in demonstrating a diverticulum in the third portion of the duodenum, and because of the herniated character of its structure, often into the body of the pancreas, as well as a dependence on the fluoroscopic examination for the demonstration of a lesion which may have a very narrow neck, and depend for its filling upon the activity of the duodenum, the actual incidence of pouches is difficult to determine. So many have been reported from autopsy studies, with accurate location of the pouch that, for lack of definite evidence to the contrary, we may conclude that once formed the pouches are permanent. An X-ray demonstration of diverticulum without ulcer does not vitiate the probability of their common association unless the past history, associated psychic pattern, and body type also speak against the diagnosis of ulcer.

From the data obtained in reported cases and my own observations, it may be said that a typical clinical picture of duodenal ulcer occurs in about two-thirds of the cases of diverticulum. It is not unlikely that in these cases the same mechanism is at work as that producing the symptoms of duodenal ulcer, namely, a motor disturbance at the pyloric region, as described by Turner. On the same basis the evidence suggests rather strongly that the "primary" or false diverticulum is commonly produced by a motor disfunction in the duodenum and is usually seen in long standing cases of peptic ulcer. The secondary, or true type, of course, always is associated with ulcer. Whether a diverticulum can be said to be a complication of ulcer is not easily decided, since ulcers have been seen in di-



Fig. 3

Fig. 3. Same patient as in Fig. 2. This exposure shows diverticulum with stalk, arising from third portion of duodenum.

TABLE I

| Author and Reference                  | Age of Patient | Sex | Location of Diverticulum | Remarks                                        |
|---------------------------------------|----------------|-----|--------------------------|------------------------------------------------|
| Dennis (5)                            | 60             | F   | 1st portion              | Ulcer and diverticulum                         |
| Lagoutte (8)                          | 37             | M   | 1st portion              | Ulcer and diverticulum                         |
| Sennett (12)                          |                |     |                          | Ulcer and diverticulum                         |
| Spriggs (11)                          | 51             | M   |                          | Gastric and duodenal ulcer                     |
| Spriggs (16)                          |                |     |                          | Hematemesis 3 times in 23 years                |
| Davis (19)                            |                |     |                          | Carcinoma stomach on basis of ulcers           |
| Gask (28)                             | 37             | M   | 2nd portion              | Ulcer and diverticulum                         |
| Penhallow (21)                        | 58             | M   | 1st portion              | Healed ulcer and diverticulum                  |
| Jones (22)                            | 31             | M   | 1st portion              | Ulcer and diverticulum                         |
| Macleann (23)                         | 44             | F   |                          | Partial obstruction of duodenum                |
| Gibbon (9)                            | 44             |     |                          | Two cases accompanied by peptic ulcer          |
| Nazel (2)                             |                |     |                          | Fourteen cases accompanied by peptic ulcer     |
| Cole (7)                              |                |     |                          | Three cases accompanied by peptic ulcer        |
| Ritchie (24)                          | 35             | F   | 2nd portion              | Duodenal ulcer                                 |
| Heymann (25)                          | 44             | M   | 2nd portion              | Symptoms began nt age 16                       |
| Marchison (26)                        |                | M   | 1st portion              | Ulcer and diverticulum                         |
| Butler (27)                           |                |     | 1st and 2nd portions     | Two ulcers in duodenum (operated)              |
| McQuay (28)                           | 28             | M   | 1st portion              |                                                |
| McQuay (24)                           | 65             | M   |                          | Cholelithiasis and ruptured ulcer              |
| McQuay (24)                           | 68             | M   | 1st portion              | Operated                                       |
| McQuay (28)                           | 58             | M   | 3rd portion              | Previous ulcer                                 |
| McQuay (24)                           | 51             | F   | 2nd portion              | Ulcer and diverticulum                         |
| McQuay (24)                           | 78             | F   | 2nd portion              | Operated                                       |
| (Author's Cases)<br>(History Numbers) |                |     |                          |                                                |
| 152023                                | 60             | M   | 2nd portion              | (Ulcer and diverticulum)                       |
| 231029                                | 48             | M   | 2nd portion              | Forty-six year history of ulcer and mel na     |
| 160993                                | 67             | M   | 1st portion              | Five year history                              |
| 135473                                | 49             | M   | 2nd portion              | Ulcer and diverticulum                         |
| 207716                                | 43             | M   | 3rd portion              | Ulcer and gall stones                          |
| 171628                                | 39             | F   | 1st portion              |                                                |
| 20629                                 | 58             | M   | 2nd portion              | Old ulcer operated                             |
| 311647                                | 34             | M   | 2nd portion              | Gastric and duodenal ulcers                    |
| 209918                                | 50             | M   | 3rd portion              | Prepyloric ulcer                               |
| 272-21                                | 72             | M   | 2nd portion              | Gastric and duodenal ulcers found nt operation |
| 325756                                |                | F   | 3rd portion              | Carcinomatous ulcer of stomach                 |
| 316824                                | 54             | F   | 3rd portion              | Large duodenal ulcer                           |
| 284170                                | 64             | M   | 2nd portion              | See Plate 1                                    |

verticula, a diverticulitis is possible, emptying of the pouch may be delayed and a vicious circle of irritability established. In a few instances certainly the diverticulum acts prominently as a complicating factor in producing epigastric discomfort.

When the symptoms in any given case are those of duodenal ulcer, and a diverticulum is demonstrated by X-ray, a more careful survey of the life of the patient often will lead to the diagnosis of ulcer; however, if diverticulum is demonstrated in a case not suspected of being ulcer, it is more than likely that the diverticulum is not causing symptoms and a further study for reflex or functional causes of the symptoms must be made. Such lesions may be any of a large number responsible for pylorospasm including other diseases of the duodenum. These observations naturally follow from the original statement of Turner, and if

acted upon, a clearer understanding of the basis of symptoms will follow.

### CONCLUSION

(1) Clinical evidence suggests that diverticula of the duodenum are associated with reflex changes in the motility of that organ and are secondary to ulcer as the commonest lesion in this region.

(2) The most usual symptoms and signs accompanying the Roentgen demonstration of duodenal diverticulum, regardless of its site, are similar to those of duodenal ulcer, and frequently are accompanied by pylorospasm. There is no evidence that the diverticulum itself causes these symptoms.

(3) In all cases it is best to consider the diverticulum as secondary to pylorospasm and to search carefully for disease or reflex disturbances before treating the lesion as a primary one.

### REFERENCES

1. Oliver, P. N. B.: *Brit. Jour. Surg.*, 17:522-517, 1930.
2. Nazel, G. W.: *Arch. Surg.*, 11:529, 1925.
3. Bercaud, R., and Vasselle, P.: *Arch. d. mal. de l'app. digestif.*, 16:756, Oct., 1925.
4. Claiborn, P., and Sching, H. R.: *Deutsche Ztsch. Chir.*, 159: 732-761.
5. Davis, M. R.: *Lyon Chir.*, 36:321, May-June, 1933.
6. Spriggs, E. L., and Marxer, O. A.: *Brit. Med. Jour.*, 1:139-131, 1926.
7. Cole, L. G., and Roberts, Dudley: *S. G. and O.*, 31:576, Oct., 1929.
8. Fiedler, Karl, Julius, and Feldmann, Maurice: *J. A. M. A.*, 103: 2557, Dec. 29, 1934.
9. Gibbon, W. H.: *Pedology*, 21:451, Nov., 1933.
10. Edwards, H. C.: *Lancet*, 1:169, Jan. 27, 1934.
11. Spriggs, E. L.: *Brit. Jour. Surg.*, 1:181-22, 1921-22.
12. Spriggs, E. L.: *South African Med. Jour.*, 3:145, Jan. 27, 1934.
13. Tarnowski, S.: *Arch. d. Medec.*, 9:1631, Jan. 31, 1934.
14. Case, James T.: *J. A. M. A.*, 75:1463, Nov. 27, 1926.
15. Kellogg, Edward L.: *The Duodenum*, 1933, Paul Hoeber, New York.
16. Perry, E. C., and Shaw, L. L.: *Guy's Hosp. Reports*, 50:175, 1893.
17. Linammyer, H.: *Verh. deutsch. path. Gesellsch.*, 17:445-455, 1914.
18. Lagoutte et Rousselin, L.: *Lyon Chir.*, 30:347, May-June, 1933.
19. Davis, K. S.: *Cal. and West. Med.*, 39:229-234, Oct., 1933.
20. Gask, G. E.: *Brit. Jour. Surg.*, 21:155, July, 1933.
21. Penhallow, D. P.: *J. A. M. A.*, 80:1372-1374, May 12, 1923.
22. Jones, W. M.: *J. A. M. A.*, 78:1796, June 3, 1922.
23. Macleann, N. J.: *Am. Surg.*, 85:153, Jan., 1927.
24. Ritchie, H. P., and McWhorter, G. L.: *S. G. and O.*, 27:105, Nov., 1917.
25. Heymann, E.: *Berlin Klin. Woch.*, 54:1032-1933, Oct. 22, 1917.
26. Marchison, D. R.: *J. A. M. A.*, 75:1329, Nov. 13, 1926.
27. Butler, P. T., and Ritvo, M.: *Boston Med. and Surg. Jour.*, 162: 765, April 9, 1925.
28. McQuay, R. W.: *Am. Surg.*, 89:25, Jan., 1929.

## SECTION II—*Experimental Physiology*

### The Mechanism of the Delay in Gastric Emptying Time Caused by Anoxemia\*

By

GEORGE CRISLER, Ph.D., M.D., E. J. VAN LIERE, Ph.D., M.D.

and

I. A. WILES, M.S.

MORGANTOWN, WEST VIRGINIA

IN previous communications (1), (2), we have reported that anoxemia causes a delay in the evacuation of the stomach. Although marked individual variations in the response of different animals to anoxemia were observed, most animals manifested some delay at 560 mm. of pressure and only one out of 29 dogs failed to show delay at 450 mm. of pressure. The findings naturally raised the question of the mechanism of the delay.

It seemed logical to start the investigation for answering this question by determining the effect of anoxemia on the pyloric sphincter. Also, since the vagi are predominantly concerned with the motor mechanism of the sphincter we directed our attention to these nerves. Further, vagospasm from anoxemia has been demonstrated by Eyster and Meek (3), Greene and Gilbert (4), Van Liere and Crisler (5) and others. All of this work was focused on the relation of the vagus to the heart under anoxemia, though Greene (6), suggested that the effect might be expected in its relation to the gut. We, therefore, originally suggested that anoxemia causes a vagospasm which leads to a pylorospasm which in turn is the actual cause of the slowed emptying. In some "acute" experiments performed in the meantime (7), we found that anoxemia, produced by 10 per cent oxygen or less in the inspired air of anesthetized dogs, invariably caused a fall in tone and a decrease in the amplitude of contractions of the filled stomach. The data in this paper show that the effect of anoxemia on the emptying of the stomach may be divided, depending upon the severity of the anoxemia, into those attributable to the pylorospasm, as we suggested, and into those attributable to a decreased motility of the stomach.

#### METHOD

Normal and control anoxic gastric emptying times were established in 14 dogs. The diet and experimental procedure were those reported in our former paper (2). The degrees of anoxemia used were 760, 560, 450 and 360 mm. of pressure corresponding respectively with 20.96, 15.45, 12.75 and 9.94 per cent oxygen and to 0; 8,200; 13,750 and 19,265 feet in altitude. The animals were then subjected

to various operative and experimental conditions and corresponding emptying times were determined. Throughout this paper we have called the emptying time at 760 mm. before operation, "the normal emptying time", and after the various operations, "the postoperative normal". Some animals were used for more than one procedure so that more than fourteen individual series of experiments were performed. In nine animals the pyloric sphincter effectively was obliterated, as checked at autopsy, by pyloroplasty (Rammstedt's operation). In two of four dogs the pyloric outlet was supplemented by a posterior gastro-enterostomy and in the other two it was excluded, the pylorus being ligated at the time of the performance of the gastro-enterostomy. In four animals 1/100 gr. of atropine was given just before each test in the experimental series at various degrees of anoxemia. In one animal the vagus fibers to the pylorus were sectioned by making a circular incision around the stomach down to the mucosa about 1 cm. proximal to the pyloric orifice, the muscular layers being held together by four anchor stitches which served to prevent undue retraction of the cut structures. While this procedure probably does not deprive the more distal portion of the pylorus, including the sphincter, of all of its parasympathetic innervation, it does interrupt most of the fibers and the results were clear enough that we may assume we were dealing with complete parasympathetic denervation.

#### RESULTS

The animals in the present series make the individual variations in the normal emptying times between different animals more apparent than ever, so that in most of the tables we have expressed the effect in terms of 100 per cent for the normal emptying time and for the postoperative normal. This serves to make the variations of different animals apparent only under experimental anoxic conditions while the variations in the normal emptying times before and after experimental operative procedures are concealed. The numbers in the tables represent the average of a number of tests in each case. Because we determined the emptying times to a + or -15 minutes only, the accuracy of our tables is within about 8 per cent; hence, a change of less than this amount is insignificant unless all values vary in the same direction.

*Effects of operative procedures per se.* In Fig. 1 the results of a typical animal in each group are shown in hours. It will be noted that after the various opera-

\*From Department of Physiology, West Virginia University, Morgantown.  
Submitted February 5, 1935.

tions the stomach usually emptied slightly more slowly than normally at 760 mm. The animals were studied long enough after operation to rule out the effects of

TABLE I.

*Selected representative animals showing emptying times at various grades of anoxemia, A. before and after pyloroplasty in terms of per cent of normal, B. before and after gastro-enterostomy, C. before and after 1/100 gr. of atropine in hours and D. before and after parasympathetic denervation of the pylorus in hours and in terms of per cent of normal. In dogs B II and B III the pylorus was also ligated at the time of operation*

| Dog No.                                          | 760 mm. pr.<br>20.96 % O <sub>2</sub> .<br>0 ft. alt. |       | 560 mm. pr.<br>15.45 % O <sub>2</sub> .<br>8,200 ft. |       | 450 mm. pr.<br>12.75 % O <sub>2</sub> .<br>13,750 ft. |       | 360 mm. pr.<br>9.94 % O <sub>2</sub> .<br>19,265 ft. |       |
|--------------------------------------------------|-------------------------------------------------------|-------|------------------------------------------------------|-------|-------------------------------------------------------|-------|------------------------------------------------------|-------|
|                                                  | Before                                                | After | Before                                               | After | Before                                                | After | Before                                               | After |
| <b>A. Pyloroplasty</b>                           |                                                       |       |                                                      |       |                                                       |       |                                                      |       |
| I                                                | 100                                                   | 100   | 123                                                  | 83    | 174                                                   | 125   | 249                                                  | 184   |
| II                                               | 100                                                   | 100   | 139                                                  | 95    | 154                                                   | 116   | 335                                                  | 267   |
| III                                              | 100                                                   | 100   | 120                                                  | 99    | 230                                                   | 107   | 259                                                  | 189   |
| IV                                               | 100                                                   | 100   | 118                                                  | 80    | 234                                                   | 94    | 310                                                  | 194   |
| V                                                | 100                                                   | 100   | 112                                                  | 79    | 167                                                   | 89    | 331                                                  | 147   |
| <b>B. Gastro-enterostomy</b>                     |                                                       |       |                                                      |       |                                                       |       |                                                      |       |
| I                                                | 100                                                   | 100   | 132                                                  | 92    | 152                                                   | 102   | 246                                                  | 130   |
| II                                               | 100                                                   | 100   | 123                                                  | 97    | 175                                                   | 98    | 248                                                  | 101   |
| III                                              | 100                                                   | 100   |                                                      |       | 204                                                   | 93    |                                                      |       |
| IV                                               | 100                                                   | 100   |                                                      |       | 135                                                   | 126   |                                                      |       |
| <b>C. Atropine</b>                               |                                                       |       |                                                      |       |                                                       |       |                                                      |       |
| I                                                | 6.55                                                  | 8.27  | 11rs.                                                | 11rs. | 10.00                                                 | 13. + |                                                      | 11rs. |
| II                                               | 6.54                                                  | 9.00  |                                                      |       | 8.50                                                  | 12.00 |                                                      |       |
| III                                              | 7.06                                                  | 10.41 |                                                      |       | 9.85                                                  | 12.00 |                                                      |       |
| IV                                               |                                                       |       | 7.25                                                 | 9.50  |                                                       |       |                                                      |       |
| <b>D. Parasympathetic denervation of pylorus</b> |                                                       |       |                                                      |       |                                                       |       |                                                      |       |
| I                                                | 5.95                                                  | 6.30  | 6.55                                                 | 5.50  | 9.37                                                  | 6.25  | 13.50                                                | 11.62 |
|                                                  | 100                                                   | 100   | 95                                                   | 87    | 160                                                   | 99    | 231                                                  | 184   |

postoperative convalescence. These results will be dealt with at length in another paper.

**Pyloroplasty.** After pyloroplasty and under anoxemia the stomach did not empty more slowly than the postoperative normal until a stage of anoxemia well below that causing slower emptying before operation was reached. In fact, after the operation at 560 mm. the stomach emptied faster than the postoperative normal, in spite of the fact that it emptied slower than the normal at 560 mm. before operation. At 450 mm. the stomach emptied essentially in the postoperative normal time, there being both increases and decreases with an average of 106 per cent, which is not significant when compared with the slower emptying that resulted in every case before operation. At 360 mm. the stomach emptied slower than the respective normal emptying time both before and after operation although the delay was much more marked before operation. These results are summarized in Table 1A.

**Gastro-enterostomy.** In two animals tested at 560 mm. the stomachs emptied slower than normal before the gastro-enterostomy was performed and suggested faster than the postoperative normal afterwards. At 450 mm. the stomachs of all the animals emptied slower than the normal before operation while in only one case did they empty slower than the postoperative normal after operation. Thus 450 mm. does not as a rule cause slower emptying after gastro-enterostomy. In the two dogs tested at 360 mm. the stomach still did not empty slower than the postoperative normal in one,

while in the other it did empty more slowly after operation but the retardation was not nearly of the same magnitude as before operation. These results are summarized in Table 1B.

**Atropine.** Atropine caused the stomachs to empty slower in every case. The normal emptying time was delayed 26 to 47 per cent and the delay at 450 mm. was approximately of the same magnitude. The delay in the normal emptying time with atropine could not, however, be used to foretell the magnitude of the delay under anoxemia with atropine. (See Table 1C).

**Parasympathetic denervation.** In the one animal with an almost completely parasympathetically denervated pyloric sphincter, results very similar to those for pyloroplasty and gastro-enterostomy were obtained. The animal was one of the rather rare ones whose stomach emptied faster than normally at 560 mm. before operation, but after denervation it emptied still faster. At 450 mm. the stomach emptied distinctly slower than normal before operation, while it emptied in the postoperative normal time after operation. At 360 mm. more marked slowing occurred before than after operation. After completion of the data on this animal, as a check on the efficacy of the denervation, the peripheral end of the vagus was stimulated under ether. The typical pylorospasm did not occur and at autopsy scar tissue forming a bridge across the suture line was found, but time had not been allowed for any functional vagus regeneration. These results are summarized in Table 1D.

## DISCUSSION

We now have a series of 29 dogs all of whose stomachs emptied more slowly during anoxemia, confirming our previous report on 6 animals. We never have had a dog whose stomach failed to show the delay at some stage of anoxemia. The threshold for the delay in most animals lies around a pressure of 560 mm. (15 per cent oxygen), though three animals showed faster emptying at this grade of anoxemia. If vago-spasm is the mechanism involved in the delay, one might reason that the motor effect of the vagus on the stomach in these exceptional cases is prepotent over its motor effect on the pylorus.

The removal of the pylorus by operative section left the emptying time of the stomach dependent upon its own motility, there being no impediment to the outgoing food. In this instance reducing the pressure to 450 mm. (12.75 per cent oxygen) usually did not delay evacuation. When the pylorus was replaced or supplemented by gastro-enterostomy the same effects obtained. These results indicate that in the less severe grades of anoxemia the stomach empties slower because of pylorospasm, for it empties slower before pyloroplasty and gastro-enterostomy but in the postoperative normal time afterwards. It should be re-emphasized that the threshold values for anoxemia vary with different animals so that it is possible for one animal to give the same sort of response at 450 mm. pressure as another would at 360. As a rule, however, we consider the threshold before operation to be 560 mm. and after operation 450 mm. That is, if the pylorus can be thrown into spasm, the stomach will empty slower at pressures between 560 and 450 mm. because of the spasm. When pressures below 450 mm. are used then the stomach empties slower, partially or entirely, depending upon whether the pylorus is functional or not, because of decreased stomach motility.

Atropine cannot be used to test the presence of vagospastic pylorospasm for the motor fibers to the stomach as well as those to the pylorus are paralyzed. Such a paralysis of the motor fibers to the stomach causes it to empty slower as has been shown by Fetter, Barron and Carlson (8), and other authors and most recently redemonstrated by Meek and Herron (9).

It seemed to us that the only way to denervate the pylorus parasympathetically without disturbing the vagus innervation to the stomach was to cut the fibers intramurally in the manner described above. Atropine and vagus nerve section could not be relied upon. The animal in which this was done (Table 1D, Fig. 1D.) acted in every way similar to the animals with pyloroplasty and gastro-enterostomy. As already pointed out there may still be a remnant of parasympathetic innervation to such a pylorus, but it is of no consequence. Thus, we have concluded that our hypothesis is essentially correct, namely that anoxemic pylorospasm is on a vagospastic basis and accounts for the delayed evacuation resulting from reduced pressures down to a certain range (450 mm. in most animals). This conclusion is further supported by the fact that after the retarding influence of a vagospastic pylorus on gastric evacuation was removed, regardless of how it was done, the stomachs of all the animals emptied faster than the postoperative normal at a pressure of 560 mm. and some of them even at a pressure of 450 mm. This we interpret as meaning that when the vagus stimulation is prevented from

at this grade). These findings indicate that the delay at 360 mm. in an unoperated animal has a complex genesis, only part of it being explained by the vagospastic pylorospasm. Other additive causes may be the direct effect of anoxemia on the smooth musculature of the stomach, a stimulation of the sympathetics with a tendency to depress stomach motility, a liberation of adrenalin tending to inhibit the stomach through stimulation of the sympathetics, or a combination of any or all of these. One is also led to speculate as to the part *sympathin* might play. The invariable fall in tone and decrease in amplitude of contractions of the filled stomach, which we reported to result from anoxemia (7), were obtained in anesthetized dogs with 10 per cent oxygen or less. These results harmonize with our present results on unanesthetized animals, because 10 per cent oxygen corresponds to about 360 mm. of pressure, and indicate that decreased motility of the stomach is the additional cause of its slower emptying when subjected to severe grades of anoxemia.

In another paper (Van Liere, Crisler and Wiles, in press) we have reported the effects of anoxemia on the pylorus of anesthetized dogs. In such experiments we were unable to predict what the effect might be, because, even in the same animal at different times, we obtained opposite results. Sometimes a tendency towards a pylorospasm was abolished by double vagotomy, and sometimes it persisted afterwards. We concluded that the diversity of results was to be explain-

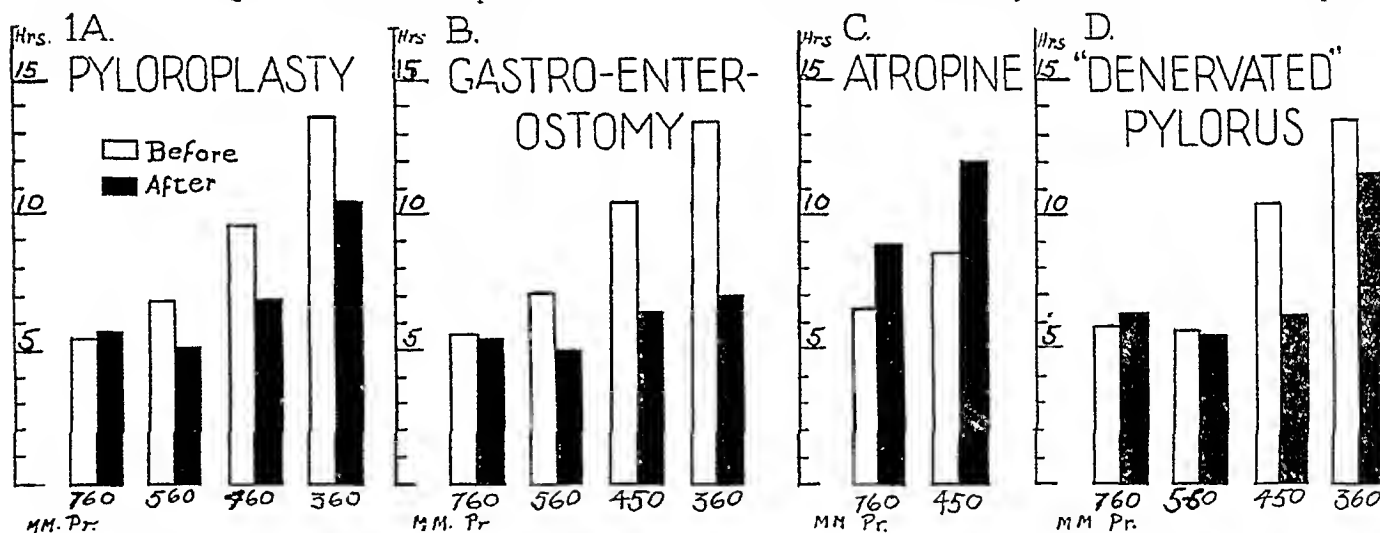


Fig. 1. A typical dog in each case showing the influence of A. pyloroplasty, B. gastro-enterostomy, C. atropine and D. parasympathetic denervation of the pylorus on the emptying times of the stomach in hours under various degrees of anoxemia. Note that the postoperative normal emptying time is, if anything, slightly longer than the normal emptying time (760 mm. before operation). The animal in B. is the only one in the entire series which showed a shortened emptying time after operation at 760 mm. and it is not significant. Note also the invariably shorter emptying time at 560 than at 760 mm. after operation (A, B and D). The dog in D. is also exceptional in that his emptying time at 560 mm. before operation was shorter than at 760 mm.

causing a pylorospasm, its motor influence on the stomach becomes manifest and causes faster than normal emptying until such severe degrees of anoxemia are reached that motility begins to suffer directly from anoxemia.

At pressures below 450 mm., such as 360, after the various operations, although the stomachs emptied distinctly slower than the postoperative normal time, they did not empty so slowly as in the corresponding tests before operation. (One dog—II in Table 1B—had such a high threshold after operation that his stomach emptied in the postoperative normal time even

ed on the basis of the complex control of the pylorus and upon the multiplicity of the stimuli produced by anoxemia. Thus, as is well known, other factors than vagus stimulation may cause pylorospasm. It is possible that more severe grades of anoxemia may cause pylorospasm irrespective of the vagi, which may be a partial cause of the delayed emptying at a pressure of 360 mm. We are inclined, however, to disregard this possibility in our experiments on unanesthetized dogs because the percentage delay at 360 mm. in the animals in which pylorospasm was prevented by pylorus section (in which emptying was solely a factor of the

motility of the stomach) was greater than those in which the pylorus was still functional but supplemented by gastro-enterostomy. Because of the consistency of our results on unanesthetized dogs, we are prepared to conclude that under mild degrees of anoxemia the delay in gastric evacuation is due chiefly to a vagospastic pylorospasm, and that under severe degrees of anoxemia a decreased motility of the stomach operates additively.

### SUMMARY

1. Studies on 23 additional dogs have entirely confirmed our previous reports showing that anoxemia causes a delay in gastric evacuation.

2. Removing, replacing or supplementing the pylorus prevents the delay caused by the less severe grades of anoxemia. This indicates that the delay resulting from mild anoxemia is due to pylorospasm. The more severe grades of anoxemia cause additional

delay probably by directly depressing the motility of the stomach.

3. The pylorospasm is on a vagospastic basis since it disappears when the vagus fibers to the pylorus are cut without disturbing those to the stomach. Atropine cannot be used for this demonstration because it simultaneously depresses the motility of the stomach.

4. After removal or denervation of the pylorus mild anoxemia may cause faster evacuation because the vagospastic effect on gastric motility now becomes manifest. However, the postoperative normal emptying time is not shorter than the normal (760 mm.).

5. We conclude that the delay in gastric emptying time during anoxemia is at first, i. e., until a critical threshold is reached, upon a vagospastic pylorospastic basis. After this threshold is passed additional delay is caused by a loss in gastric motility.

### REFERENCES

1. Crisler, G., and Van Liere, E. J.: The Effect of Anoxemia on the Emptying Time of the Stomach. *Am. J. Physiol.*, 101:26, June, 1932.
2. Van Liere, E. J.; Crisler, G., and Robinson, D.: Effect of Anoxemia on the Emptying Time of the Stomach. *Arch. Int. Med.*, 51:796, May, 1933.
3. Eyster, J. A. E., and Meek, W. J.: Experiments on the Origin and Propagation of the Impulse in the Heart. *Heart*, 5:119, 137, 227, 1914.
4. Greene, C. W., and Gilbert, N. C.: Studies on the Response of the Circulation to Low Oxygen Tension: VI. The Cause of the Changes Observed in the Heart During Extreme Anoxemia. *Am. J. Physiol.*, 50:155, March, 1922.
5. Van Liere, E. J., and Crisler, G.: A Study of Vagospasm: The Action of the Vagus on the Heart During Acute Anoxemia. *Am. J. Physiol.*, 105:469, August, 1933.
6. Greene, C. W.: Oxygen Supply and Metabolic Level. *The Medical Herald and Physiotherapist*, Kansas City, Mo., May, 1926.
7. Crisler, G.; Van Liere, E. J., and Booher, W. T.: The Effect of Anoxemia on the Digestive Movements of the Stomach. *Am. J. Physiol.*, 102:629, December, 1932.
8. Fetter, D.; Barron, L., and Carlson, A. J.: The Effect of Induced Hyperthyroidism on the Gastro-Intestinal Motility of Vagotomized Dogs. *Am. J. Physiol.*, 101:505, September, 1932.
9. Meek, W. J., and Herron, R. C.: The Effect of Vagotomy on Gastric Emptying Time. *Am. J. Physiol.*, 109:221, August, 1934.

## Quantitative Estimation of Enzyme Concentration in Duodenal Fluids: A Practical Clinical Method\*

By

CHARLES W. LUEDERS, M.D.  
PHILADELPHIA, PENNSYLVANIA

THE procedure for the determination of tryptic and lipolytic activity in duodenal fluids has been greatly modified as to simplicity of method in comparison with that published by us in a previous paper (1). The first method was studied last year by the Committee on a survey of the enzyme tests as performed by members of the American Gastro-Enterological Association (2). The Committee overlooked a later article by Watson and myself, read before the Association and published in 1932 (3), in which were embodied these new modifications for the estimation of tryptic and lipolytic concentration in duodenal fluids. In theory the newer method will later be shown to better satisfy essential laws of enzyme action; in practice, over a period of four years, it has proved itself a simple, rapid clinical method, which confines accurate normal values within narrow range, provides a sharp division between high and low concentration, and records abnormal values in diseased states, especially of the pancreas, liver, gall-bladder; also in

undernutrition and disorders of digestion and assimilation. The original method of amylase determination, by the estimation of maltose formed by hydrolysis of a given amount of soluble starch, using Benedict's reagent, has, with but slight modification, proved clinically satisfactory during the past fifteen years.

It is possible that a wider use of the newer method applied to normal groups may prove to other clinicians its value, and eventually overcome the objection of the Committee to the older method when they state (2): "The Lueders system is more accurate, relatively simple, but may be objected to on theoretical grounds." The newer method is in fact a modification by Hollander (5) of our previous method. It is accepted by me as such.

In my own opinion the chief theoretical objection to our previous method for trypsin and lipase determinations, was the attempt to record quantitatively the amount of amino and fatty acids formed in an hour's digestion period in terms of the number of c. c. of N 10 Na OH required to restore neutrality to the mix-

\*From the Laboratory and Gastro-Intestinal Clinic of the Pennsylvania Hospital.  
Submitted January 21, 1934.



ture. Now the "factor of reversibility of reaction" during hydrolysis by enzymes is most important, since enzymes like trypsin and lipase combine with the end products of the substrate, (combined amino and fatty acids), and act in opposition to the initial reactions. These two opposing processes of hydrolysis and synthesis act to produce an equilibrium. In the hydrolysis of starch by amylase, the "factor of reversibility" is negligible but instead a direct linear proportionality exists between the amount of enzyme present and the amount of hydrolysis effected.

The newer method set forth below rules out the factor of reversibility of reaction during hydrolysis by trypsin and lipase through an estimation of *concentration* rather than *amount*, and expressed in minutes or fractions thereof required for the neutralization of 1 c. c. of tenth normal sodium hydroxide by the amino and fatty acids formed by the hydrolysis respectively of gelatin and olive oil emulsions. Trypsin and lipase are both active in a neutral or slightly alkaline substrate. The addition of the 1 c. c. of tenth normal sodium hydroxide does not change the hydrogen ion concentration of the mixture sufficiently to inhibit the enzyme except in very low concentration. The technic takes into consideration this possibility and I believe avoids it. The time required for the formed amino and fatty acids to neutralize the added sodium hydroxide is inversely proportional to the concentration of the hydrolyzing enzymes trypsin and lipase. This result may readily be checked by using 4 different amounts of the same sample of duodenal fluid i. e. 1 c. c.; 0.5 c. c.; 0.25 c. c.; 0.125 c. c. added to each of 4 tubes of proper neutral substrate with a further addition of 1 c. c. of decinormal sodium hydroxide. The time required to change the deep phenolphthalein red to neutral (with a control) will be found to be in inverse ratio to the amount of the duodenal fluid (1 c. c. or less), or in other words in inverse ratio to the concentration of the enzyme.

It was Bayliss (4) who first stressed the universal rule found to govern the action of the hydrolyzing enzymes, namely the "Time Law" of Hedin: "To obtain the same effect with varying amounts of an enzyme, the time of digestion must vary inversely with the concentration of the enzyme." Hollander (5) applied this law in a modification of our method during 1930 and stated: "In quantitative determinations of reversible reactions especially it is more accurate to measure the time taken to effect a definite change than the amount of change in a definite time." As mentioned above the "Time Law" of Hedin does not apply to the quantitative estimation of amylolytic activity.

This modified technic was first applied by me during a study of the effect of insulin injections upon pancreatic enzymes in malnutrition. (3). Tests for the separate enzymes will here be set up in procedure form so that they may more readily be followed by the clinician or his assistant.

#### PROCEDURE

**Collection of Samples.** Follow the regular Lyon technic for duodenal drainage with a few departures as here outlined:

1. Patient must not swallow saliva during test. Provide small pus basin.
2. Extract gastric contents. Test for free HCl. If the addition of 1 drop of Topfer's reagent fails to produce a deep red color to gastric extraction, introduce through

tube 100 c. c. of 0.5 per cent HCl (to attempt to destroy salivary amylase). Retain 5 minutes, patient recumbent.

3. Then permit gravity return flow of the acid and gastric juice throughout the 20 minute gradual swallowing of tube to the 70 cm. mark.

4. If possible never use syringe for collection of duodenal samples; gravity return the safe and correct method.

5. When tube has passed to the 70 cm. mark, a bile tinged fluid (duodenal residue) should appear. Collect in small test tube surrounded by ice. If free HCl is present discard at once, then allow drainage to flow into fresh tube; repeat until sample contains no free HCl. Collect 10 c. c. of a crystal clear sample. If unsuccessful, pass 50 c. c. of hot water through tube, permit immediate return, which frequently effects a bile stained duodenal fluid return. Mark sample "A". Keep on ice until tested.

6. Give a half stimulation: 37.5 cc. of 33 per cent  $MgSO_4$ . Clip tube, wait 5 minutes. When return flow becomes dark coffee and crystal clear collect 10 c. c. in tube surrounded with ice. Mark tube "B". Collect sample "C" in same manner. If returns are cloudy turn patient on back.

7. Discard all samples that have free HCl or a total acidity of over 0.2N/10. Estimate enzymes at once, keeping tubes surrounded by ice. Or keep in Ice Chest.

**Tryptic Activity.** Trypsin is estimated as to concentration and expressed in minutes and fractions thereof, required for 0.5 c. c. of duodenal fluid to neutralize 1 c. c. of N/10 Na OH, when both are added to a neutral emulsion of 5 per cent gelatin (rendered pink with phenolphthalein as indicator. (a1) A normal tryptic activity will, within five minutes, produce amino-acids sufficient to render neutral the mixture, with loss of pink coloration.

1. Add 25 c. c. of neutral 5 per cent emulsion of gelatin to each of four large test tubes marked "A", "B", "C" and "X". "X" is the control. To the latter add 1 c. c. of boiled duodenal fluid of either "A" or "B" fraction. (Heat destroys enzyme).

2. Place in transparent water bath (\*) preferably with copper tube rack, above microburner. Maintain temperature of solutions in tubes between 37 and 40° C.

3. Add the exact amount of N/10 NaOH to equalize the low acidity of 0.5 c. c. of the duodenal fluid samples "A", "B" and "C".

4. Add 0.5 c. c. of each duodenal fluid sample to the proper tube. Note the exact time for each addition.

5. Remove each tube, place palm over end, shake and return quickly to waterbath.

6. Add 0.5 c. c. of N/10 NaOH to tubes "A", "B" and "C" and shake.

7. When dark pink changes to light pink add final 0.5 c. c. of N/10 NaOH to each tube and shake.

8. Note the exact time when the pink color disappears from the three solutions, or tends to match the solution in the control tube "X".

9. Subtract starting times in Step No. 4 from neutralization times in Step No. 8. Concentration of tryptic activity for each sample is expressed therefore in minutes and fractions thereof, and is inversely proportional to the time; i. e. the shorter the time, the greater the concentration.

**Lipolytic Activity.** Lipase is estimated as to its concentration and expressed in minutes and fractions thereof required for 0.1 c. c. of duodenal fluid to neutralize 1 c. c. of N/10 NaOH, when both are added to a neutral emulsion of 20 per cent olive oil (b2), rendered pink with phenolphthalein (1 per cent alcoholic solution) as indicator. A normal lipolytic activity, will within five minutes or less, produce fatty acids sufficient in concentration to render the solution neutral or free from the pink coloration.

\*For a transparent water bath use a 2 to 4 liter pyrex beaker; insert a circular copper test tube rack with holes to support 6 or more large test tubes of at least 5 cc. capacity. Set on high tripod above a microburner. Temperature of 37 to 40° C in the test tube may also be maintained by the addition of hot water to the water bath, as required.

tion. If neutralization takes longer than five minutes 0.5 c. c. of duodenal fluid instead of 0.1 c. c. is used but the reduced time figures are multiplied by five.

1. Add 25 c. c. of neutral emulsion of 20 per cent olive oil to each of four tubes marked "A", "B", "C" and "X". "X" is the control. To the latter add 1 c. c. of boiled duodenal fluid of either "A" or "B" fraction. (Heat destroys enzyme.)

2. Place in transparent water bath, preferably with copper tube rack, and keep temperature of solutions between 37 and 40° C. with micro-burner.

3. Add the exact amount of N 10 NaOH to equalize the low acidity of the duodenal fluid. (Estimate exact amount by testing acidity of 1 c. c. of the sample, and add to solution one half of reading if 0.5 c. c. of duodenal fluid is used). Make no adjustment for 0.1 c. c. duodenal fluid.

4. Add 0.1 c. c. of duodenal samples to proper tubes, shake and return to bath. Note exact time that each duodenal sample is added to substrate.

5. Wait three minutes exactly. (See note 3 below). Pink color may disappear.

6. Add 0.5 c. c. of N 10 NaOH to tubes "A", "B" and "C". A deep pink color may appear.

7. When mixture completely loses its pink color, add the final 0.5 c. c. N 10 NaOH and shake.

8. Note exact time when color in each of the "A", "B" and "C" tubes matches the color of the control tube "X".

9. Subtract starting times in Step No. 4 from neutralization times in Step No. 8. Concentration of lipolytic activity for each sample is expressed in minutes and fractions thereof.

Note 1. If neutralization time is 10 minutes or over, repeat the test but use 0.5 c. c. of duodenal fluid, and multiply the shorter time figure by five.

Note 2. If upon addition of the second 0.5 c. c. of N 10 NaOH no pink coloration recurs, the ferment concentration is less than three minutes. Repeat the test adding the 2 half portions of the 1 c. c. of N/10NaOH within the first minute of digestion.

Note 3. This method has shown that lipase is about five times more active than trypsin, hence the use of but 0.1 c. c. duodenal fluid. Lipase is more sensitive to N 10 NaOH than is trypsin. When amounts as low as 0.1 c. c. of duodenal fluid are tested, one can conceive of a dilution of ferment so great that 1 c. c. of N/10 NaOH might weaken its activity, or even destroy it, even aside from the inhibiting power of the increased pH. The three minute wait permits the ferment to act in a neutral or weakly acid mixture (formed fatty acids). Although many duodenal fluids have a lipolytic ferment in high concentration, i. e. in only 0.1 c. c. of duodenal fluid, a larger study of normals may bring a further modification in the technic, namely, the use of 0.5 c. c. of duodenal fluid for both tryptic and lipolytic activity.

**Amylolytic Activity.** Amylase is determined quantitatively by estimating the maltose formed by the action of 1 c. c. of duodenal fluid on 20 c. c. of a 5 per cent solution of potato starch (c3) made neutral or faintly pink with phenolphthalein (0.2 per cent alcoholic solution) as indicator. The end point is yellow white to a light gray. Past the end point a deepening pink appears. Since the above amount of substrate contains one gram of starch, the total amount of maltose formed in one hour will be a fraction of a gram. Bergeim (6) states that actual hydrolysis seldom exceeds 80 per cent of the theoretical 1.056 gms. of maltose in 1 gm. of starch. Willstätter considers 75 per cent the limit of saccharification.

In the Conversion Table for Total Maltose, normal hydrolysis of starch by this test, may be judged to lie

TABLE I  
Conversion for Total Maltose

| Normal Hydrolysis    |                      | Poor Hydrolysis      |                      |
|----------------------|----------------------|----------------------|----------------------|
| Buret reading in cc. | Maltose in Gm. and % | Buret reading in cc. | Maltose in Gm. and % |
| 0.3*                 | 0.99                 | 1.1                  | 0.27                 |
| 0.4                  | 0.74                 | 1.2                  | 0.25                 |
| 0.5                  | 0.60                 | 1.3                  | 0.23                 |
| 0.6                  | 0.50                 | 1.4                  | 0.21                 |
| 0.7                  | 0.42                 | 1.5                  | 0.20                 |
| 0.8                  | 0.37                 | 1.6                  | 0.19                 |
| 0.9                  | 0.33                 | 1.7                  | 0.17                 |
| 1.0                  | 0.30                 | 1.8                  | 0.16                 |

\*The conversion of 1 gm. of starch to 0.99 gm. of maltose is exceptional. Readings lower than 0.3 cc. would suggest the presence of salivary amylase or intestinal maltase in sufficient quantities to vitiate this or any method based on determination of reducing sugar. (6).

within the figures of the first maltose column; poor hydrolysis within the figures of the second column.

The most valuable and instructive work upon comparative tests for pancreatic amylase is that of Schmidt, Greengard and Ivy which appeared recently in this Journal (6). Constructive criticism of our method as first applied is merited; however modifications over the past ten years have corrected most of them.

The possible advantages of this test and its technic over other recommended tests is 1. simplicity; 2. reagents more commonly in use in most laboratories; 3. and of essential importance: the recognition that salivary amylase is still active in duodenal fluids in cases of hypochlorhydria and achylia; 4. the technic tends to reduce this serious complication to a minimum. A possible disadvantage: The end point, always a clear cut change from the Benedict reagent blue to a yellow or grayish white, is frequently shortened as further substrate is added, producing a deepening pink.

Bergeim (7) confirms my own doubts about the value of any test for pancreatic amylase in cases of achylia. The latest writers who recommend the newer tests for pancreatic amylase do not seem to have considered the question of saliva. In Bergeim's words: "the gravest criticism of any method for estimating pancreatizing amylase" . . . "It is on this account, evidently, that it is necessary to determine trypsin and lipase."

#### Procedure.

1. Add 20 c. c. of the 5 per cent starch solution (c3) to each of three large test tubes marked "A", "B" and "C". Also the same amount to control tube "X".

2. To each tube add one drop of 0.2 per cent alcoholic solution phenolphthalein. (\*) Then add, drop by drop, N 1 NaOH until a light pink color is produced which persists on shaking. 1 or 2 gts. usually.

3. Now add to each tube, drop by drop, from a burette, N 10 H<sub>2</sub>SO<sub>4</sub> until the first disappearance of the pink color. (\*\*). Immerse tubes in hot water until solutions are heated to 37° C.

4. Add 1 cc. of each duodenal fluid sample to the proper "A", "B" and "C" tube. Add 1 cc. of boiled "B" sample to Control tube "X". Incubate tubes for one hour at 37°C., shaking the tubes every 15 minutes.

5. Upon removal from incubator add to tubes "A", "B"

(\*) Note. Dr. Bergeim advises the weak solution of phenolphthalein to insure an exact end point, and avoid the deep red color after the gray-white.

(\*\*) Note. The pH for maximum activity of amylase is on the acid side of neutrality or 6.5. The loss of pink color with N/10 H<sub>2</sub>SO<sub>4</sub> measures (approximately) neutrality (pH 7.4); the addition of the weakly acid duodenal fluid gives a still lower pH concentration sufficiently accurate in practice to permit maximum amylolytic activity. pH 7.0 by test.

TABLE II  
Normal Findings for Trypsin and Lipase in 35 Normal Subjects (Hollander)

| Patient                | Lipase<br>Minutes | Trypsin,<br>Minutes |
|------------------------|-------------------|---------------------|
| D. A.                  | 2                 | 4                   |
| A. B.                  | 2½                | 3                   |
| M. C.                  | 3                 | 2                   |
| H. E.                  | 1½                | 3                   |
| J. E.                  | 5                 | 5                   |
| S. F.                  | 3                 | 5                   |
| R. G.                  | 4½                | 5                   |
| B. G.                  | 2                 | 1                   |
| E. G.                  | 4                 | 3                   |
| Repeated 2 weeks later | 5                 | 4½                  |
| A. G.                  | 3                 | 2                   |
| E. S.                  | 2½                | 3½                  |
| M. J.                  | 4½                | 4½                  |
| A. K.                  | 1½                | 2½                  |
| F. K.                  | 1                 | 1                   |
| Repeated 1 month later | 2½                | 3                   |
| S. L.                  | 3½                | 5                   |
| B. L.                  | 5                 | 5                   |
| E. M.                  | 1                 | 1½                  |
| H. N.                  | 5                 | 5                   |
| J. C.                  | 2                 | 2½                  |
| M. O.                  | 1                 | 2                   |
| I. P.                  | 5                 | 5                   |
| E. R.                  | 3½                | 4½                  |
| C. W.                  | 4                 | 2½                  |
| W. W.                  | 2½                | 3                   |
| A. T.                  | 5                 | 4                   |
| N. S.                  | 3½                | 2                   |
| C. S.                  | 1                 | 4½                  |
| S. S.                  | 3½                | 5                   |
| B. S.                  | 1½                | 1½                  |
| Repeated 3 weeks later | 1½                | 1½                  |
| 5 weeks later          | 5                 | 3                   |
| 7 weeks later          | 2½                | 5                   |
| 9 weeks later          | 1½                | 2                   |
| H. C.                  | 1½                | 3                   |
| M. C.                  | 3½                | 4                   |
| B. D.                  | 1½                | 2½                  |
| M. G.                  | 2                 | 2½                  |
| I. G.                  | 1½                | 1½                  |
| Repeated 1 day later   | 2                 | 2                   |

and "C" a small amount of sodium carbonate (about 5 grains), to stop digestion.

6. Pour a portion of each digestion mixture into its proper 2 c. c. pipette, (used as a burette), and graduated in tenths, and run slowly (0.2 c. c.), then drop by drop, in 5 c. c. of Benedict's reagent (d4) plus 1-2 gms. of sodium carbonate (½ in. of spatula) heated to boiling in 25 c. c. Erlenmeyer flask, over micro burner. (Add previously a pinch of powdered talc to prevent bubbling).

7. End Point. Boil gently until the last blue color disappears and changes to yellow or slate gray, and before the gray changes to pink the end point is reached.

8. Result. Expressed quantitatively in terms of maltose. The burette reading divided into 0.0149 (the number of grams of maltose to reduce 5 cc. of Benedict's reagent) gives the amount of maltose in 1 cc. of the digestion mixture. Multiply by 20 to obtain the total amount of maltose formed from 1 gm. of starch. (See conversion table above).  $0.0149 \div \text{burette reading} \times 20 = \text{gms. of maltose.}$

a1. 5 Per Cent Gelatin Emulsion. Dissolve 25 grams of sheet-gelatin\* in 300 c. c. distilled water in 500 c. c. pyrex flask set in a water bath. Raise temperature gradually until gelatin is perfectly dissolved and clear. In a mortar place 12.5 gms. of gum acacia (purest grade), add gradually 50 c. c. of liquid albolene, rub into a smooth paste, then add all at once, 25 c. c. of distilled water and continue stirring in one direction until a milk white emulsion is formed. To this add the 300 c. c. of melted gelatin. Pour into a graduated cylinder. Make up to 500 c. c. with washings of mortar and warm distilled water, and 2 c. c. of 1 per cent alcoholic solution of phenolphthalein made neutral with normal NaOH. Shake well, then distribute into 100 c. c. storage flasks. Cover the emulsion in the flasks with a thin layer of toluene; store in ice chest. When needed liquify by gentle heat in water bath; (a temperature of 60° C will scorch gelatin). "Shake well" label on

flasks, to insure an even emulsion before measuring into test tubes marked 25 c. c.

b2. 20 Per Cent Olive Oil Emulsion. Place 25 gms. of gum acacia (purest grade) in a mortar; add gradually 100 c. c. of highest quality olive oil; rub into a smooth paste; then add all at once 50 c. c. of distilled water, and continue stirring in one direction until a milk white emulsion is formed. Add more distilled water; make up to 500 c. c. in a graduated cylinder, using washings of mortar with distilled water. Pour into a 500 c. c. flask. Add 2 c. c. of 1 per cent alcoholic solution of phenolphthalein and make neutral (faint pink) with Normal NaOH (about 1.5 c. c.). Shake Well Label on flask, to insure an even emulsion before pipetting into test tubes. Keep in ice chest. A 50% emulsion is more stable. See "Equipment."

After considerable experiment it was found that dependable results were obtained only with freshly prepared oil emulsion. Formaldehyde as a preservative was not satisfactory; toluene with the oil emulsion gave larger figures for time or negative results. Sterilization also proved unsatisfactory. 20% emulsion stable 1 mo. 50% much longer.

c3. Starch Solution (5 per cent). Stir 25 gms. of Merck's soluble starch (Lintner) into a smooth paste in a mortar by adding slowly 30 c. c. of cold distilled water. Heat to boiling 470 c. c. of distilled water in a 500 c. c. sterile pyrex flask. Pour gradually into starch paste, stirring continuously to insure a mixture free from lumps. Pour the solution back into the warm pyrex flask. Add five milligrams of mercuric iodide to the 500 c. c. mixture (10 mgm. to the liter), as a preservative. It is preferable to the toluene previously used; it prevents lumping of the starch. May be kept on ice or at room temperature.

d4. Benedict's sugar reagent

Copper sulphate (crystallized)..... 18.0 grams  
Sodium carbonate (crystallized) (one half the weight of the anhydrous salt may be used)..... 200.0 grams  
Sodium or Potassium citrate..... 200.0 grams  
Potassium thiocyanate..... 125.0 grams  
Potassium ferrocyanide (5 per cent solution) ..... 5.0 cc.  
Distilled water to make a total volume of ..... 1000.0 cc.

With the aid of heat dissolve the carbonate, citrate and thiocyanate in enough water to make about 800 cc. of the mixture and filter if necessary. Dissolve the copper sulphate separately in about 100 cc. of water and pour slowly into the other liquid with constant stirring. Add the ferrocyanide solution, cool, and dilute to exactly 1 liter. The copper salt only, need be weighed with exactness.

Duodenal Juice Of Highest Concentration. The above technic allows for the testing of the three duo-

TABLE III  
Normal Enzyme Findings After Course of Insulin in Patients With Previously Abnormal Enzyme Concentration (Lueders and Watson)

| Patient         | Trypsin,<br>Minutes | Lipase,<br>Minutes | Amylase,<br>Maltose, Gm. |
|-----------------|---------------------|--------------------|--------------------------|
| H. S.           | 1½                  | 3½                 | 1.20 (error)             |
| One week later  | 1½                  | 3                  | 0.80                     |
| Two weeks later | 4½                  | 5½                 | 0.60                     |
| C. B.           | 2½                  | 2½                 | 0.60                     |
| J. C.           | 1                   | 4                  | 0.60                     |
| One week later  | 2                   | 7 (abnormal)       | 0.55                     |
| C. P.           | 3                   | 3                  | 0.60                     |
| One week later  | 3½                  | 3                  | 0.60                     |
| E. F.           | 1½                  | 2½                 | 0.42                     |
| M. M.           | 5½                  | 4¾                 | 0.37                     |

\*Gelatin, for culture media, sheet form, Pfanstiehl, 1 lb., \$2.50.

TABLE IV  
Enzyme Concentration in Five Cases of Diabetes.  
(Lueders and Watson)

| Case No. | Trypsin, Minutes |     |     | Lipase, Minutes |     |     | Amylase, Maltose, Gm. |      |      |
|----------|------------------|-----|-----|-----------------|-----|-----|-----------------------|------|------|
|          | "A"              | "B" | "C" | "A"             | "B" | "C" | "A"                   | "B"  | "C"  |
| 1.       | 9                | 20  | 14½ | 4½              | 6   | 4½  | 0.27                  | 0.14 | 0.23 |
| 2.       | 20               | 12  | 0   | 16½             | 10½ | 30  | 0.15                  | 0.19 | 0.00 |
| 3.       | 40               | 0   | 20  | 27½             | 12  | 4½  | 0.30                  | 0.15 | 0.25 |
| 4.       | 3½               | 5½  | 13  | 4½              | 4½  | 4½  | 0.35                  | 0.25 | 0.27 |
| 5.       | 10               | 15  | 12  | 3½              | 3½  | 3½  | 0.35                  | 0.23 | 0.21 |

denal fractions, "A", "B" and "C". Friedenwald, Einhorn and Bockus agree that the fasting duodenal juice represents the highest point of enzyme concentration. Hollander found the specimen having the deepest color following the instillation of 33 per cent magnesium sulphate solution contained the pancreatic ferments in highest concentration. After reviewing the hundreds of tests performed before the final procedure was accepted as of clinical value, I find that sample "C" contains usually ferments of lower concentration; that sample "B" (darkest colored fluid after salt stimulation) and sample "A" (duodenal residue or common duet fluid or their combination) are equally rich in pancreatic ferments; but for clinical work I prefer sample "B", and for two reasons: 1. less possibility of salivary amylase; 2. the increased bile salts in the "B" mixture insures maximum activation of lipase and protection of amylase from destruction by trypsin. Granted that magnesium sulphate stimulates the secretion of intestinal maltase this factor of error in any test for pancreatic amylase is of minor importance as compared with the likely presence of salivary amylase in duodenal residue, (sample "A").

*Normal Values Of Enzyme Concentration.* To judge the value of a method for estimation of ferment activity, figures established as normal should have been derived from tests upon normal subjects. Normal figures should be confined within narrow limits. The method should reveal a sharp division between the high concentration of enzymes in health and the low concentration of the same enzymes in certain diseases, especially of organs concerned in the functions of digestion, assimilation and nutrition. The Committee

"on survey of enzyme tests etc." of the American Gastro-Enterological Association has asked certain members of the Association to compare the Willstätter method for estimation of amylolytic activity with the Lueders method, by estimating the amylase in the duodenal contents on twenty normal individuals, or persons known not to have diseases involving the G-I tract, applying both methods. Trypsin and lipase concentration, using our own method, will be estimated at the same time the above request of the Committee is carried out in our own group.

The five minute limit for normal concentration of lipase and trypsin using but 0.1 c. c. of duodenal fluid for lipolytic activity, and but 0.5 c. c. for tryptic activity very effectively isolates all duodenal fluids with low concentration. In my own experiments upon patients with diseases of the digestive tract and with those suffering from undernutrition, few of them consistently recorded a figure within the 5 minute limit. Hollander's findings were as striking. I shall include a table of figures of enzyme concentration for trypsin and lipase in his normal subjects using this modification of our first method, the same modification I have applied for the past four years, and the technic of which is presented above.

As for the accuracy and practical value of the amylase quantitative test first applied by us in 1922, so many preliminary studies were made on duodenal fluids from healthy subjects as well as patients with diseases of the G-I tract, that it was then established that 1 c. c. of duodenal fluid in health should convert 1 gm. of potato starch, incubated at 37° C, into maltose, to the extent of 0.8 gm. Patients suffering from

TABLE V  
Enzyme Concentration in Cases With G-I Tract Disorders or Diseases

| Case No. | Diagnosis                                 | Trypsin, Minutes |     |     | Lipase, Minutes |     |     | Amylase, maltose gm. |     |     |
|----------|-------------------------------------------|------------------|-----|-----|-----------------|-----|-----|----------------------|-----|-----|
|          |                                           | "A"              | "B" | "C" | "A"             | "B" | "C" | "A"                  | "B" | "C" |
| 1.       | Giardiasis                                | 7                | 5   | 5½  | 3½              | 2   | 3   | .42                  | .42 | .37 |
| 2.       | Gall Bladder Adhesions                    | 0                | 22½ | 5½  | 0               | 3   | 3   | .40                  | .19 | .30 |
| 3.       | Hypochlorhydria                           | 9½               | 7   | 7½  | 3½              | 3   | 3   | .37                  | .42 | .37 |
| 4.       | Hypochlorhydria                           | 4½               | 4½  | 4½  | 3               | 3   | 3   | .37                  | .21 | .15 |
| 5.       | Gall Bladder Adhesions, atasis            | 0                | 7   | 12  | 4½              | 3   | 3½  | .40                  | .27 | .27 |
| 6.       | Chronic Eczema Gall Bladder Obstruction   |                  | 10  |     |                 | 15  |     |                      | .37 |     |
| 7.       | Amebiasis, prediabetes                    | (wk. later)      | 3   |     |                 | 12  |     |                      | .46 |     |
|          |                                           |                  | 4   |     |                 | 15  |     |                      | .60 |     |
| 8.       | Achylia; gastric tumor                    | (wk. later)      | 2   |     |                 | 7½  |     |                      | .32 |     |
|          |                                           |                  | 4½  |     |                 | 12  |     |                      | .50 |     |
| 9.       | Achylia, old growth with duodenal fistula |                  | 4½  |     |                 | 20+ |     |                      | .33 |     |
|          |                                           |                  | 4½  |     |                 | 20+ |     |                      | .60 |     |
| 10.      | Scurvy; prediabetic                       |                  | 3   |     |                 | 20+ |     |                      | .21 |     |
|          |                                           | (wk. later)      | 8½  |     |                 | 20+ |     |                      | .19 |     |
| 11.      | Pericious Anemia                          |                  | 2½  |     |                 | 12  |     |                      | .42 |     |
|          |                                           | (wk. later)      | 3   |     |                 | 2   |     |                      | .50 |     |
| 12.      | Cholecystitis, giardiasis                 |                  | 2½  |     |                 | 7½  |     |                      | .37 |     |
|          |                                           | (wk. later)      | 4½  |     |                 | 20+ |     |                      | .50 |     |
| 13.      | Acute Cholecystitis                       |                  | 7½  |     |                 | 6   |     |                      | .27 |     |
| 14.      | Achylia, hyperthyroidism                  |                  | 3½  |     |                 | 20+ |     |                      | .60 |     |
|          |                                           |                  | 6½  |     |                 | 20+ |     |                      | .42 |     |

digestive tract disorders did not give that percentage of hydrolysis. Therefore figures below 0.3 gm. of maltose are considered abnormal.

After years of personal experience with enzyme tests in the chemical laboratory, hospital and office, I am willing to predict that no routine ferment analyses will become popular with the internist unless it proves simple in method and materials, rapid in technic and whose sufficient accuracy is dependent not so much upon complicated buffers, optimum pH, and formulae as upon the expression of a mean between necessarily wide fluctuations of enzyme concentrations in the heterogeneous mixture known as duodenal fluid.

### COMMENT

In spite of the fact that normal values for enzyme concentration were occasionally found in one or more of the duodenal fractions of the diseased group, it was rare to obtain normal concentration of the three enzymes as in the normal groups. As revealed in Table 4, although five cases are too few on which to base conclusions, it is of interest that in each case of diabetes the pancreatic amylase was low in amount, and in every extraction of duodenal fluid. I repeat, that the above methods applied clinically during the past four years have restored a faith in the clinical value of routine pancreatic ferment estimations, which all previous methods, including our own, had well nigh destroyed.

### CONCLUSIONS

Methods are described for the determination of trypsin, lipase and amylase in duodenal fluids. Modification by Hollander of our previous methods for estimation of tryptic and lipolytic activity has proved of distinct value during the past four years of its application. The test for amylase, with but slight modification, has proved satisfactory during the past fifteen years. Any clinician trained in the Lyon technic of non-surgical duodenal drainage should find the above methods simple, rapid and sufficiently accurate. As soon as some such practical procedure for the estimation of pancreatic enzymes in duodenal fluids has been widely accepted as reliable it may well give fresh impetus to further investigation of secretory dysfunction and diseases of the pancreas. It should also prove a valuable routine addition to the diagnostic survey of patients with any disease involving the G-I tract as well as those with disorders of nutrition, digestion and assimilation.

I wish to here express my sincere appreciation of the valuable advice and criticism by Dr. O. Bergeim, in re-

cent correspondence as to improvements in our amylase test. Also heartfelt thanks to Miss M. E. Watson for her kindness in her latest check up of all the data accumulated during the application of the above methods upon hundreds of duodenal fluids studied in 1931.

### EQUIPMENT FOR TESTS

#### Glassware

- ½ doz. small test tubes (½ in. diam.)
- ½ doz. large test tubes (1 in. diam.)
- ½ doz. small beakers (250 cc.) (or drinking cup or glass)
- One large Beaker, Pyrex (2-4 liter)
- ½ doz. small Erlenmeyer flasks (50 cc.)
- 2 CC. Pipette (graduated in tenths cc. Use as burette)
- 2 Pipettes, volumetric (25 cc.)
- 1 Pipette, volumetric (5 cc.)
- 1 CC. Pipette, graduated in tenths cc.)
- 1 Cylinder (250 cc. graduated)

#### Chemicals

- Phenolphthalein 1% and 0.2% (alcoholic sol.)
- NaOH, N/10 and N/1
- HCl, (USP.) To make 0.5% sol.
- Sodium Carbonate
- Powdered Talc
- Benedict's Reagent
- Gelatin (5 per cent emulsion)
- Starch (5 per cent solution)
- Olive Oil (20% emulsion) (\*) (Last four solutions prepared as described in body of paper)
- H<sub>2</sub>SO<sub>4</sub>, N/10

#### Miscellaneous

- 1 Copper circular test tube rack
- 1 Tripod (high) to support large Beaker
- 1 Micro-burner
- 1 Centigrade thermometer
- 1 Glass dropper tip, rubber tube and clip to attach to end of 2 cc. Pipette
- 1 Small Incubator (gas or electric)

*Note.* Most of the miscellaneous equipment may be dispensed with, if the clinician has a large pitcher of hot water available to keep adding to the water, in the large beaker, surrounding the digestion mixtures so that the temperature in each test tube is maintained at 37 to 40° C for the duration of the test.

*Note\*:* Olive Oil Emulsion (50%) machine made, may be purchased from Abbott Laboratories, North Chicago, Ill. Preferred by Dr. Crandall in his Lipase test (8). Also from J. Wyeth & Bro., Phila. If 50% Emulsion is used, 10 c. e. is diluted to 25 c. e. with distilled water for test.

### REFERENCES

1. Lueders, C. W.; Bergeim, O., and Rehfuess, M. E.: Quantative Determination of Enzyme Activity in Duodenal Fluids. *Am. J. M. Sc.*, 166:535, Oct., 1923.
2. Transactions. 1934: American Gastro-Enterological Association; p. 38.
3. Lueders, C. W., and Watson, M. E.: The Effect of Insulin Therapy on Pancreatic Enzymes in Malnutrition. *Arch. Int. Med.*, 49:330, Feb., 1932.
4. Bayliss, Sir W. M.: The Nature of Enzyme Action. London, 1925.
5. Hollander, E., and Marcus, J. M.: Pancreatic Function: 1. The Quantitative Determination of Pancreatic Enzymes. *Arch. Int. Med.*, 36:585, Oct., 1925. Hollander, E.: A Clinical Method for the Quantitative Determination of Pancreatic Ferments in Duodenal Contents. *J. Lab and Clin. Med.*, 16:460, Feb., 1931.
6. Schmidt, C. R.; Greengard, H., and Ivy, A. C.: A Comparison of Methods for the Quantitative Estimation of Diastase in Duodenal Fluid. *Amer. Jour. Digestive Diseases and Nutrition*, 1:9, Nov., 1934.
7. Bergeim, O., Dept. of Physiol. Chem., College of Med. Univ. of Illinois. Correspondence: Nov. and Dec., 1934.
8. Crandall: *Amer. Jour. Physiol.*, 100:266, 1932.

# The Origin and Significance of the Blood Serum Enzymes\*

By

LATHAN A. CRANDALL, Jr., M.D., Ph.D.  
CHICAGO, ILLINOIS

THE value of the quantitative determination of blood (serum) enzymes, especially amylase (diastase), in the diagnosis of pancreatic disease has been established. There are also many reports in the literature on the use of other enzyme determinations as aids in diagnostic procedure; in most cases these have not been adequately confirmed and their value is speculative. Our knowledge of the origin, fate, and significance of the serum enzymes in health and disease is fragmentary, and for the most part is based upon assumptions rather than conclusive evidence. In many cases we cannot even be certain of the significance of changes which are well beyond the limits of normal. Certain confusions in terminology and a multiplicity of methods have produced conflicting reports; to this is added a lack of established normal standards, due largely to technical difficulties.

A review of those facts which are of practical significance will therefore be presented, together with certain pertinent experimental data.

## THE ENZYMES OF NORMAL BLOOD

Blood serum is known to contain ferments acting upon the three major classes of foodstuffs: carbohydrates, lipoids, and proteins. The enzyme acting upon carbohydrates is the starch and glycogen splitting ferment termed amylase or diastase; it seems probable that more than one type of amylase is present. Sera from animals of different species certainly show wide variations in their ability to attack various starches (1). In man, variable results are obtained, depending upon whether one studies the ability of the enzyme to produce sugars, its capacity to split the starch to the point where iodine no longer gives a blue color, or the change in viscosity brought about in a starch solution. Until more conclusive evidence is available concerning the nature of these enzymes, and the fractions of starch which they attack, it will probably be most satisfactory to refer to the reducing sugar producing enzyme as "saccharogenic amylase," and to that which causes the change in viscosity as "liquefying amylase."

The general term "esterase" signifies those enzymes capable of hydrolyzing the ester linkage. It covers the group that attacks such various compounds as ethyl butyrate, tributyrin, true fats and oils, cholesterol esters, lecithin, and the waxes. An esterase or esterases acting upon ethyl butyrate are present in blood and in all tissues examined (2). The word "lipase" is often used synonymously with esterase, or may be restricted to the enzyme (or enzymes) capable of splitting true fats and oils at the ester linkage. Since the oil splitting ferments have been shown to be quite distinct from those hydrolyzing the simpler esters, it is

perhaps best to use lipase in the second, more limited, meaning. In this sense there is seldom any appreciable amount of lipase (active on fats and oils) in normal human sera, although as will be noted later it may be present in certain pathological conditions. The esterases which are present in blood and which act upon ethyl butyrate or tributyrin are inactive upon true fats or oils such as olive oil. Confusion in the nomenclature of the lipolytic enzymes is probably best avoided by employing a term suggestive of the specific substrate used, i.e., "lecithinase," "ethyl butyrase," "tributyrinase," etc., reserving *lipase* for the enzymes active on neutral fat (triglycerides of the higher fatty acids).

Relatively little attention has been paid to the proteases of the blood. The determination of the proteolytic activity of serum is complicated by the presence of anti-proteases. Recent studies (3) have shown that accurate determination of serum proteases is possible only when they have been adsorbed on a protein and thus freed from anti-proteases. Since no clinical studies of the serum proteases in which this factor is considered have been encountered in the literature, a discussion of these enzymes is not pertinent to the material presented herein.

In addition to the three classes of enzymes mentioned above, the blood contains phosphatase, catalase, histaminase, possibly maltase, and a number of other specific enzymes. With the exception of phosphatase little is known of the variations of these ferments in pathological conditions. The increase in serum phosphatase that occurs in diseases of the bone has been shown to be of diagnostic value (4).

## METHODS

A detailed discussion of the methods employed in the estimation of blood enzymes is not within the province of this article. It should be emphasized, however, that many of the apparently contradictory results reported in the literature may be explained by variations in the procedures used by different investigators.

In the case of the amylases the method of Wohlgemuth (5), which depends upon the failure of starch to give a blue color with iodine after hydrolysis, has been frequently employed. This procedure is subject to rather large variations, depending upon the technique and color judgment of the individual, and the starch sample used as the substrate. It has therefore been largely supplanted by less subjective methods, notably the viscometric (determination of viscosity changes in an autoclaved starch substrate) which was first applied to amylase by Davison (6), and the group of methods that depend upon determination of the reducing sugar liberated from starch. The two latter methods are approximately equal in accuracy, although

\*From the Department of Physiology and Pharmacology, Northwestern University Medical School, Chicago, Illinois.  
Submitted March 15, 1925.



both require considerable attention to the elimination of interfering factors. The evidence in the literature suggests that either different enzymes or different properties of the same enzyme are measured, depending upon whether one estimates the early stages of starch hydrolysis (viscometric or Wohlgemuth methods) or the amount of end products formed (reducing sugar liberated).

Even when only one method is employed, differences in the type of starch used as substrate will produce considerable variation in the results (7). This may be due to varying amounts of amylose, amylopectin, and dextrins in the starch sample. According to Somogyi (8) the amylase of blood serum splits starch chiefly to tri-saccharides which have reducing properties, only a small amount of maltose being formed. He states that maltase does not appear to be present in serum. In view of the differing reducing powers of glucose, maltose, and tri-saccharides, the presence or absence of maltase and of enzymes which split the tri-saccharides may introduce appreciable errors in the determination of saccharogenic amylase. In the determination of liquefying amylase by the viscometric

TABLE I

*Lipase and diastase in portal and saphenous blood after intravenous injection of 30 cc. pancreatic juice. London cannula on portal vein*

|                           | Saphenous |          | Portal |          |
|---------------------------|-----------|----------|--------|----------|
|                           | Lipase    | Diastase | Lipase | Diastase |
| 1:00                      | 0.0       | 9.       | 0.0    | 10       |
| Injected pancreatic juice |           |          |        |          |
| 1:15                      | 1.0       | 61       | 1.7    | 69       |
| 1:45                      | 1.0       | 40       | 1.5    | 48       |

method the presence or absence of ferments which attack maltose or trisaccharides is of course immaterial. With all amylase methods, however, considerable variation in results will appear unless precautions are taken to keep the substrate constant in composition or to determine the effect of substances which may be present in solution with the enzyme. It is especially important to maintain the pH and salt concentration constant.

In order to insure uniformity of results when various lots of substrate must be used, a simple and reliable procedure is to take advantage of the stability of enzymes in 50% glycerin. A preparation of ground pancreas, pancreatin, or pancreatic juice in 50% glycerin will usually remain constant in activity for several months; one such preparation of pancreatin kept in

the icebox showed no change over a period of two years with regard to its lipase content. Amylase is similarly stable in glycerin. Such a preparation may be used as a standard, for the comparison of various lots of substrate. In any event the arbitrary "units" which must be employed in expressing enzyme activity will usually vary from one laboratory to another, due to unavoidable variations in the substrate.

The methods for the determination of the esterases usually involve titration of the fatty acids set free by action of the enzyme on the substrate in the presence of a buffer. The principal variation in the results obtained by different workers is due to the different substrates employed. Many workers have considered the enzyme which attacks ethyl butyrate or tributyrin to be identical with that which hydrolyzes the true fats, and have used the term "lipase" for both. Cherry and Crandall (7) have recently shown that these two enzymes are quite distinct, and have suggested that the term "esterase" be employed for the former, "lipase" for the latter. The blood ordinarily contains appreciable amount of esterase but little or no lipase. The amount of esterase (ethyl butyrase) in pancreatic juice is not far from that in the blood, but this secretion contains relatively enormous amounts of lipase (olive oil substrate). When the pancreatic ducts are ligated the esterase content of the blood may rise or fall slightly or may not change, while lipase appears in the blood in large amounts. Since many workers have employed ethyl butyrate or tributyrin in the determination of lipolytic activity in pancreatic juice or duodenal drainage, statements concerning the "lipase" activity of these fluids must be interpreted on the basis of the method employed. Esterase is an ubiquitous enzyme, occurring in every tissue examined. Lipase is not present in striated muscle, brain, lung, or blood serum; the liver and spleen contain a small amount, the pancreas yields the greatest quantity, and intestinal mucosa is intermediate. There is no reason to assume that esterase is manufactured by the pancreas, the amounts found in pancreatic juice might well be present in any secretion formed from the blood plasma. The high concentration of esterase found in the liver suggests that this organ is the chief site of its formation. On the other hand, the pancreas may with equal logic be presumed to generate lipase, although no inference can be drawn regarding the ability of other organs to form this enzyme.

#### THE RELATION OF BLOOD ENZYMES TO PANCREATIC FUNCTION

The significance of blood amylase in the diagnosis of pancreatic disease has been the subject of many reports; the literature has been reviewed recently by

TABLE II

*The effect of injecting secretin intravenously on the serum lipase and diastase in Eck fistula dogs. One unit secretin equals minimal amount necessary to obtain a response from the pancreas of a normal dog.*

| Secretin |            | Control |        | 45 min. |     | 2 hrs. |     | 3 hrs. |     | 4 hrs. |     |
|----------|------------|---------|--------|---------|-----|--------|-----|--------|-----|--------|-----|
| Dog      | Units inj. | Lipase  | Diast. | Li.     | Di. | Li.    | Di. | Li.    | Di. | Li.    | Di. |
| E 28     | 80         | .2      | 11     |         |     | .7     | 13  |        |     | .1     | 10  |
| E 29     | 40         | .4      | 15     | .7      | 15  |        |     |        |     | .6     | 17  |
| E 29     | 50         | .0      | 15     |         |     | .3     | 35  |        |     |        |     |
| E 29     | 40         | .7      | 16     |         |     | .6     | 15  |        |     | .7     | 23  |
| E 30     | 25         | .5      | 12     | .4      | 15  |        |     | .8     | 19  |        |     |
| E 31     | 50         | .4      | 11     | .6      | 11  |        |     |        |     | .6     | 14  |

McCaughan (9) who also presents animal experiments illustrating the enormous rise of the blood amylase after pancreatic injury or obstruction of the pancreatic ducts. McCaughan employed the viscometric method, which because of its sensitivity and accuracy has been largely used by workers in this field. He points out that the normal range for amylase is relatively narrow. Many workers have noted the tendency of the blood amylase to return to the normal value within about two weeks after ligation of the ducts. Gould and Carlson (10) also described secondary and even tertiary rises so that the blood amylase may be above normal even 2½ months after complete duct ligation. A number of recent workers have suggested that blood enzyme determinations in the presence of pancreatic disease can be expected to be significant only within a brief period after injury, because of the rapid return to normal in animals under similar conditions. This statement is apparently based upon experiments that have been continued only until the first return of the blood enzyme to normal. The fact that a second and third rise may occur suggests that the period during which blood amylase determinations may be significant is longer than has been assumed. It is nevertheless true that in the presence of chronic injury to the pancreas the blood amylase does not remain elevated. On the basis of animal experimentation one may assume that slighter degrees of pancreatic injury will produce less marked and more brief amylase elevation. If the pathological changes in the pancreas progress to fibrosis and degeneration, the blood amylase may even fall below the normal value. Thus in early pancreatic injury the amylase of the blood may be expected to be elevated roughly in proportion to the injury, normal values do not necessarily signify a normal pancreas, while a decrease in blood amylase suggests chronic pancreatic injury with cessation of enzyme formation.

The reports concerning the effect of pancreatectomy on the blood amylase in the dog are variable. King (26) and Gould and Carlson (10) found a decrease; further literature is quoted by Reid, Quigley, and Myers (28). The writer has observed abnormally low blood amylase values on depancreatized dogs (maintained on insulin and fed raw pancreas) as long as one year after operation (viscometric method). Such findings have led many workers to conclude that the pancreas is important in maintaining the blood amylase level. Reid, Quigley, and Myers (27) state that there is a tendency for the blood amylase to fall after pancreatectomy, but that normal values are restored by insulin. They further report high amylase values in uncontrolled diabetics, using in both instances a reducing sugar method. This question is of significance because it involves the interpretation of low values found clinically. Abnormally small amounts, if found by the viscometric or starch-iodine methods, may suggest deficiency in enzyme formation by the pancreas. Interpretation of amylase values based on the reducing sugar method are more difficult. Reid and Narayana (11), using this method, find that ligation of the pancreatic ducts in dogs has no effect upon the blood amylase level. Until further studies are made, the estimation of saccharogenic amylase would seem to be of doubtful value in the diagnosis of pancreatic disease.

Conditions not involving external secretory function of the pancreas, but which may alter blood amylase,

are nephritis, liver disease, and diabetes. The values found in these conditions will depend upon whether saccharogenic or liquefying amylase is determined. In no instances, however, are more than moderate increases encountered. When a marked rise in the (liquefying) blood amylase is present it must be interpreted as indicating pancreatic pathology.

It has been known since the work of Hanriot (12), Doyon and Morel (13), and Arthus (14) that normal serum contains no enzyme capable of hydrolyzing the true fats or oils, whereas the pancreatic secretion is very active in this respect. These workers also recognized the presence of an esterase (ethyl butyrase) in the blood serum. The above facts have been largely ignored. Many investigators have made the assumption that the ethyl butyrase of the blood stream is related to the lipase of the pancreas, and that like amylase it should reflect changes in pancreatic function. The fact that the ethyl butyrase of the serum shows little or no change after pancreatic injury has led to conflicting reports. As stated above, attempts have been made to study "lipase" even in the pancreatic juice by the use of ethyl butyrate as a substrate, with obviously discrepant results. It should be noted that McClure, Wetmore and Reynolds (15) introduced the use of finely emulsified and buffered cottonseed oil in the study of lipase in the duodenal drainage, with very satisfactory results. Cherry and Crandall (8) employed a similar method (finely emulsified olive oil with buffer) in the study of serum lipase. Olive oil, peanut oil, and cottonseed oil appear to be equally satisfactory; presumably any triglyceride of the higher fatty acids will serve. Crandall and Cherry confirm previous observations on the absence of lipase (olive oil splitting) in the normal serum, and appear to be the first to have shown that such a lipase is found in the blood, in relatively large amounts, after ligation of the pancreatic ducts. Ligation of the ducts produces no constant change in the esterase acting on ethyl butyrate or tributyrin as determined by the titration or stalagmometric methods. The olive oil lipase appears in the serum within 24 hours after duct ligation and returns to normal within 2 to 6 weeks, depending apparently on the degree of injury to the pancreas. It may, like amylase, show a secondary rise. Lipase is commonly present in small but definite amounts in the serum in the presence of liver pathology, recalling the tendency of serum amylase to rise under similar conditions. This phenomenon will be discussed below; it obviously complicates the value of serum lipase determinations in the diagnosis of pancreatic disease when the liver is known to be affected. It should be noted, however, that the increases in serum lipase and amylase which occur after liver injury are relatively small, never approaching the figures found shortly after acute pancreatic obstruction. Comfort and Osterberg (16) have recently investigated the serum lipase and esterase in patients with pancreatic, hepatic, or biliary tract disease. They find abnormally high values for lipase in a large percentage of patients with acute or subacute pancreatic affections, and suggest that it be further studied as an aid in diagnosis. Esterase determinations (ethyl butyrase) were found to be of no value. In view of the accuracy, simplicity, and sensitiveness of the lipase method it deserves further clinical trial in comparison with amylase in diseases of the pancreas.

The literature on determinations of serum esterase

in disease has been reviewed by Oppenheimer (17). No studies that have appeared since this review alter the conclusion that changes in blood esterase are not associated with any disease in such a manner as to permit esterase determinations to be used as a diagnostic aid.

#### THE RELATION OF BLOOD ENZYMES TO THE LIVER

Wohlgemuth in 1910 showed that ligation of the common bile duct caused a delayed but definite rise in the blood diastase. This rise did not occur if the bile duct ligation was performed some time after ligation of the upper pancreatic duct; that is, liver damage had no effect on a blood amylase which was already increased secondary to pancreatic obstruction. Falkenhäuser (18) has shown that the blood amylase increases after phosphorus poisoning in dogs and rabbits (starch iodine method). Tomioka (19) has also reported increased blood diastase values on experimental liver damage of various types in animals and in liver disease in man. Elman, Arneson and Graham (20) did not observe increased blood amylase values in human liver disease without pancreatic involvement (viscometric method). In a preliminary report Crandall and Cherry (21) have confirmed the increase in liquefying amylase following ligation of the common bile duct, and have reported that the serum amylase is frequently above the normal level in Eck fistula dogs. The same authors (22) have observed abnormally high amylase values in liver disease.

Very recently Somogyi (23), studying saccharogenic amylase, reports only abnormally low values in liver disease. This interesting apparent difference between liquefying and saccharogenic amylases, like that found for pancreatic duct ligation, requires further investigation. Such studies are in progress.

Studying the lipolytic enzymes in experimental liver damage, Crandall and Cherry (24) have reported the appearance of (olive oil) lipase in the serum following ligation of the common bile duct or production of Eck fistula in dogs, and have noted that the esterase (ethyl butyrase) is not significantly changed under these conditions. They further found appreciable amounts of lipase in the blood of eight out of ten cases of human liver disease, as compared with positive values in only 7.6% of 131 control cases which were selected at random, and in which hepatic or pancreatic damage was not ruled out except by preliminary examination (22). Since that time the author has observed significant amounts of lipase after chloroform or cinchophen poisoning in dogs. Barker (25) has also found it present in the serum after plasmapheresis or long continued low protein diets in dogs; degenerative changes are found in the liver in these animals at autopsy.

In our preliminary report on the regulation of blood diastase and lipase by the liver, Cherry and I (21) suggested that these enzymes might normally be absorbed from the gut (presumably in small amounts) and removed from the portal blood by the liver. This might explain their appearance in the systemic blood after liver injury. It is well known that the damaged liver does not remove other substances from the blood in a normal manner. Zucker, Newburger, and Berg (27) in commenting upon this report, refer to us as supposing that pancreatic damage causes secondary liver injury, with the release of lipase and diastase from the liver into the blood. We had never enter-

tained such a conception, but suggested only that a damaged liver may be incapable of normally removing enzymes from the blood.

The reason for the increased lipase and amylase values in blood in the presence of liver disease or experimental injury is obscure. That the liver takes up enzymes from the blood is indicated by the fact that the values for amylase and lipase are higher in the portal than the systemic blood after the intravenous injection of pancreatic juice (Table I). The methods used were those discussed previously (22). It is now questionable whether there is sufficient absorption of enzymes from the intestine to influence significantly the blood enzyme values; this point will be discussed below. An attempt has been made to determine whether the secretory state of the pancreas might influence the blood lipase and amylase values in the presence of liver injury. For this purpose Eck fistula dogs were given large doses of highly purified secretin, with results as shown in Table II. The changes in the blood enzymes are in the direction of a rise in every instance; however, the changes found are not definitely beyond the normal variations of the blood enzymes.

Liver injury does not increase the lipase and liquefying amylase of the blood by reducing the amount of bile entering the intestine, since bile fistula dogs show no change in blood enzymes until the liver becomes damaged by ascending infection. It seems probable that the enzymes do not originate in degenerating liver tissue. If this were the case, one would expect high values immediately after acute injury, with gradual stabilization at or near the normal level, as is the case following pancreatic obstruction. However, the rise following experimental liver damage is never great and, at least in Eck fistula animals, may be sustained for more than a year. The principal possibilities which remain are that the liver normally regulates the blood enzyme level by removing any excess, or that pathological changes in the liver produce secondary disturbances in pancreatic function. Analyses of portal and systemic blood for amylase and lipase in normal unanesthetized dogs with London cannulae on the portal vein to collect portal blood lend no support to the first hypothesis, since even after the injection of secretin no significant portal-systemic differences were noted. It is not impossible that injury to the liver may secondarily influence the pancreas, since various types of experimental liver damage are well known to affect other parts of the gastro-intestinal tract ("peptic" ulcer after bile duct ligation, biliary fistula, Eck fistula).

One must conclude that no definite hypothesis can be formulated to explain the cause of the changes in blood enzymes (increase in liquefying amylase, appearance of olive oil lipase) in the blood in liver disease and after experimental liver injury. The slight increase in diastase found in liver disease is insufficient to be of diagnostic importance. It is possible that more extensive clinical investigations would show lipase determinations to be of some value. Somogyi's (23) observations on saccharogenic amylase should be confirmed.

Bodansky and Jaffe (29) have demonstrated an increase in serum phosphatase in dogs as a result of common bile duct ligation; the maximum value after operation was approximately 80 times the normal, which "is the highest value that we have obtained in

any condition in any animal." Roberts (30) has demonstrated an increase in phosphatase in obstructive jaundice in man, which was confirmed by Bodansky and Jaffe (29) for catarrhal jaundice. Studies of serum phosphatase in the presence of pancreatic obstruction have not been found. Simultaneous determinations of lipase (olive oil) and phosphatase in hepatic and pancreatic pathology in animals and man would be of interest, since it is conceivable that changes in these two ferments might be of more value in diagnosis than is either alone.

#### THE ABSORPTION OF ENZYMES FROM THE INTESTINE

King (26) found that the administration of 17,500 units of salivary amylase to each of 2 cats daily for 4 days resulted in an increase of 6.3 and 22.4 units in the urine, respectively. This he accepted as demonstrating the absorption of this enzyme from the gut, although it was recognized that by far the greater part must be absorbed or excreted in the feces. The absorption of amylase was denied by Zucker, Newburger, and Berg (27) who introduced pancreatic juice into the duodenum and found no increase in blood amylase. They used the starch-iodine method, which is regarded by Myers and Reid (31) as unsuited for the quantitative determination of amylase because of its inaccuracy. Zucker *et al.* further believe it unlikely that this enzyme could be absorbed because they assume it to be of the nature of a protein. It is known that even proteins may be absorbed from the intestine in traces (32); furthermore, it has been stated that it is relatively easy to prepare amylase which is protein-free (33).

In view of the above facts, further experimental work on the intestinal absorption of enzymes was undertaken. In order that the enzymes might be introduced directly into the intestine, dogs were prepared with jejunal fistulae. At a second operation Eck fistulae were established in the same animals, since if the liver is active in the removal of enzymes from the blood any increase might be more easily demonstrable after liver injury. After recovery from the operation and when in good condition these dogs then received from 200 to 300 cc. of fresh active pancreatic juice or 300 cc. of saliva (human) by way of the jejunal fistula. The results (Table III) are for the most part negative, al-

amounts of enzymes seems probable. The quantity absorbed under ordinary conditions, however, can hardly be sufficient to have any influence upon the blood enzyme level.

In view of the above facts, the hypothesis of Oelgoetz, Oelgoetz, and Wittekind (34), seems untenable. These workers suggest that enzymes, absorbed from the intestine, function in the blood stream to break down incompletely digested foods which have been likewise absorbed and that when the quantity of enzymes secreted by the pancreas is relatively insufficient for adequate digestion in the gut there is no longer an excess available for absorption as a factor of safety against unsplit food products which are also absorbed. They describe a deficiency in the serum enzymes of patients with food allergy who have been given extraordinarily large meals, and believe that the allergy may be due to the enzyme deficiency. Many studies have been made on the relation of the blood enzymes to various phases of digestion, and all workers have agreed that there is no variation with meals. The observation of Elman and McCaughan (35) that in dogs with total external pancreatic fistulae there is no decrease in blood amylase demonstrates that any deficiency of this enzyme in the blood cannot be ascribed to lack of amylase absorption. That is, absorbed amylase plays no part in maintaining the blood amylase level.

#### SUMMARY

Normal human blood contains amylases, an esterase capable of splitting ethyl butyrate or tributyrin, a proteinase (or proteinases), phosphatase, catalase, and other enzymes of less clinical significance. There is present only a trace of lipase (capable of splitting olive oil); in most cases none is found. It is pointed out that many of the variable results described in the literature may be ascribed to variations in the methods used. It seems probable that there are at least two types of amylase, one which is most active in the initial hydrolysis of the starch molecule (liquefying amylase) and another which is more effective in producing the reducing sugars that are the end products of starch digestion (saccharogenic amylase). The esterase which splits ethyl butyrate or tributyrin has frequently been termed a "lipase"; it appears preferable to reserve lipase for the enzyme active on olive

TABLE III

*The serum amylase and diastase after the introduction of pancreatic juice or saliva into the jejunum in dogs with jejunal fistulae and Eck fistulae.*

| Dog  | Amount given        | Control |       | 1 hr. |     | 2 hrs. |     | 4 hrs. |     | 6 hrs. |     |
|------|---------------------|---------|-------|-------|-----|--------|-----|--------|-----|--------|-----|
|      |                     | Lipase  | Amyl. | Lt.   | Am. | Lt.    | Am. | Lt.    | Am. | Lt.    | Am. |
| E 34 | 200 cc. pane. juice | .5      | 12    | .4    | 11  | .2     | 11  | 1.1    | 12  | 1.3    | 20  |
| E 35 | 170 cc. juice       | .4      | 16    | .3    | 13  | .2     | 14  | .4     | 14  | .3     | 15  |
| E 34 | 300 cc. juice       | .3      | 12    | .5    | 12  | .5     | 12  | .7     | 14  | .3     | 16  |
| E 35 | 300 cc. juice       | .4      | 11    | .3    | 11  | .1     | 14  | .3     | 14  | .5     | 13  |
| E 36 | 200 cc. saliva      | .2      | 9     | .2    | 9   | .1     | 15  | .2     | 16  | .2     | 12  |
| E 34 | 200 cc. saliva      | .3      | 10    | .2    | 10  | .2     | 10  | .2     | 10  | .2     | 11  |
| E 34 | 200 cc. juice       | .1      | 11    | .2    | 13  | .2     | 12  | .5     | 12  |        |     |

though in a few instances there are increases in the concentration of lipase or amylase which seem beyond the normal limits of variation. All analyses were made in duplicate by the methods previously used (22). From the evidence at hand, the absorption of minute

oil (or other triglycerides of the higher fatty acids). In acute pancreatic disease or experimental pancreatic obstruction the liquefying amylase of the blood is greatly increased; the data at present available on saccharogenic amylase show no change in this enzyme

under these conditions. At the same time blood lipase (olive oil) is also greatly increased but there is no change in the blood esterase (ethyl butyrate). In chronic pancreatic disease with failure of enzyme formation or after experimental pancreatectomy the liquefying amylase of the blood may be decreased, apparently without change in the saccharogenic amylase.

In liver disease or experimental liver injury the liquefying amylase of the blood is slightly increased in many instances. This increase is not sufficiently significant to be of clinical importance. It is reported that the saccharogenic amylase is decreased under these conditions. Clinical or experimental liver damage also results in a slight but significant increase in

serum lipase without any definite change in esterase. The serum phosphatase is also markedly elevated.

The changes in serum amylase (liquefying) are certainly of aid in the diagnosis of pancreatic disease. Further studies on lipase, phosphatase, and saccharogenic amylase may demonstrate the value of such determinations.

The possible origins of the increase in enzymes which follows liver injury is discussed.

Traces of enzymes are probably absorbed from the intestine into the blood stream. Such absorption is certainly insignificant and under normal conditions can have no effect upon the blood enzyme level.

## REFERENCES

1. Ascoli and Bonfanti: *Ztschr. f. Physiol. Chem.*, 43, 156, 1904.
2. Falk, K. G.; Noyes, H. M., and Sugiyama, K.: *Jour. Biol. Chem.*, 59, 943, 1924.
3. Kleinman, H., and Scharr, G.: *Bioch. Ztschr.*, 252, 145, 1932.
4. Kay, H. D.: *Jour. Biol. Chem.*, 89, 249, 1930.
5. Wohlgemuth, J.: *Berl. klin. Wchnschr.*, 47, 92, 1910.
6. Davison, W. C.: *Bull. Johns Hopkins Hosp.*, 37, 281, 1925.
7. Chesley, L. C.: *Jour. Biol. Chem.*, 92, 171, 1931.
8. Cherry, I. S., and Crandall, L. A.: *Amer. Jour. Physiol.*, 100, 266, 1932.
9. McCaughan, J.: *S., G., and O.*, 59, 598, 1934.
10. Gould, L. K., and Carlson, A. J.: *Amer. Jour. Physiol.*, 29, 165, 1911.
11. Reid, C., and Narayana, B.: *Quar. Jour. Exper. Physiol.*, 20, 305, 1930.
12. Hanriot, M. F. H.: *Compte. Rend. Acad. de Sci.*, 124, 778, 1897.
13. Doyon, M., and Morel, A.: *Compte. Rend. Soc. Biol.*, 54, 498, 1902.
14. Arthus, M.: *Compte. Rend. Soc. Biol.*, 54, 381, 1902.
15. McClure, C. W.; Wetmore, A. S., and Reynolds, L.: *Arch. Int. Med.*, 27, 706, 1921.
16. Comfort, M. W., and Osterberg, A. E.: *Proc. Staff Meetings, Mayo Clinic*, 9, 250, 1934.
17. Oppenheimer, C.: *Die Fermente und ihre Wirkungen*. Leipzig, 5th Ed.
18. Falkenhäusen, M. F. von: *Arch. Exper. Path. u. Pharm.*, 139, 14, 1928.
19. Tomioka, F.: *Jap. Jour. Gastroenterol.*, 2, 254, 1930.
20. Elman, R.; Arneson, N., and Graham, E. A.: *Arch. Surg.*, 19, 934, 1929.
21. Crandall, L. A., and Cherry, I. S.: *Amer. Jour. Physiol.*, 97, 515, 1931.
22. Crandall, L. A., and Cherry, I. S.: *Arch. Neurol. and Psych.*, 27, 367, 1932.
23. Somogyi, M.: *Proc. Soc. Exper. Biol. and Med.*, 32, 538, 1934.
24. Crandall, L. A., and Cherry, I. S.: *Proc. Soc. Exper. Biol. and Med.*, 28, 570, 1931.
25. Barker, H. M.: Personal communication.
26. King, C. E.: *Amer. Jour. Physiol.*, 35, 301, 1914.
27. Zucker, T. F.; Newburger, P. G., and Berg, B. N.: *Amer. Jour. Physiol.*, 102, 209, 1932.
28. Reid, E.; Quigley, J. P., and Myers, V. C.: *Jour. Biol. Chem.*, 99, 615, 1933.
29. Bodansky, A., and Jaffe, H. L.: *Proc. Soc. Exper. Biol. and Med.*, 31, 1179, 1934.
30. Roberts, W. M.: *Brit. Med. Jour.*, 1, 734, 1933.
31. Myers, V. C., and Reid, E.: *Jour. Biol. Chem.*, 99, 599, 1933.
32. Ratner, B., and Gruchl, H. L.: *Jour. Clin. Invest.*, 13, 517, 1934.
33. Waldschmidt-Leitz, E., and Reichel, M.: *Ztschr. f. Physiol. Chem.*, 204, 197, 1931-32.
34. Oelgoetz, A. W.; Oelgoetz, P. A., and Wittekind, J.: *Amer. Jour. Dig. Dis. and Nutrit.*, 1, 737, 1934.
35. Elman, R., and McCaughan, J. M.: *Arch. Int. Med.*, 40, 58, 1927.

## ABSTRACTS

STEINBERG, M. E., M.D., AND STARR, PAUL H., B.S.

*The Factor of Spasm in the Etiology of Peptic Ulcers.*  
*Arch. Surg.*, Vol. 29, No. 6, Dec., 1934, pp. 895-907.

This article is an experimental study as carried out in dogs on the relation of spasm to the etiology of peptic ulcer.

In the first group of experiments, it was shown that where the jejunum was anastomosed to the pyloric valve and the alkaline content diverted away from the gastro-jejunal anastomosis, ulcers formed with regularity in each experiment. When the same procedure was used and three-fourths of the longitudinal and circular muscles removed for a distance along the jejunum, ulcers of the pylorus developed only occasionally. No ulcers were found in that part of the jejunum where the muscle layers had been denuded. In two of the ten animals studied, in addition to the ulcers of the pylorus, there were definite ulcers formed exactly where the muscles began their intact course, or about 10 cm. from the pyloric valve. Most experimental ulcers in the jejunum arise just below the pyloric valve.

In another series of six animals, the ileum was anastomosed to a Pavlov pouch and the muscle layers in the ileum stripped for a distance of about ten centimeters. No

ulcers developed in the denuded area and one of the six animals developed an ulcer in the area just distal to the denuded portion.

In a small series of animals undergoing the Exalto short-circuiting operation, exclusion of a large distal part of the stomach and also an entero-anastomosis opposite the gastro-enterostomy, none had ulcers. Without the entero-anastomosis, ulcers were produced in 75 to 100 per cent of cases.

The *modus operandi* in these experiments which prevented the ulceration in the denuded area of the small bowel, the authors feel is due to the release of spasm by means of stripping the muscular coat. They believe that a certain degree of acidity, depending on the particular area of intestine involved causes it to contract until the degree of acidity is reduced to a certain strength, but that ulcers will not be produced without the presence of certain other factors, among them, narrowing of the lumen due to spasm.

The authors feel that these observations support the neurogenic theory as an important factor in the etiology of ulcerations of the upper gastro-intestinal tract.

N. W. Swinton, Boston.

## SECTION III—Nutrition

### Insulin-Glucose Therapy in Heart Disease\*

By

E. STERLING NICHOL, M.D.  
MIAMI, FLORIDA

#### INSULIN—GLUCOSE THERAPY IN HEART DISEASE

**I**NSULIN-Glucose Therapy in heart disease has been extolled by many foreign physicians during the past eight years, but no very favorable report on the procedure has been issued in this country. In fact, recently, this use of insulin has been called worthless, unphysiological, and even dangerous by several American authors. My own experience with the use of insulin in more than one hundred cases of malnutrition during the past seven years drowned my fear of insulin in the non-diabetic patient, and led me to the trial of insulin-glucose therapy in various types of heart disease in patients who exhibited intact carbohydrate metabolism.

Briefly, we will review (a) the facts known about the rôle of insulin and glucose in the physiology of the heart muscle (b) the effects of insulin hypoglycemia on the circulation (c) some effects of insulin in non-diabetic subjects, and (d) clinical reports relating to the use of insulin-glucose in heart disorders. My own observations on a group of 20 patients with heart disease and treated with insulin in association with glucose orally, will be reported.

#### ROLE OF INSULIN—GLUCOSE IN THE PHYSIOLOGY OF THE HEART

It is more than thirty years since first it was shown that glucose is an essential source of cardiac energy. Since then, various researches (1) have established the following facts: The heart is exacting in its glucose requirements and uses up its own glycogen before drawing on available glucose. In addition to an adequate supply of glucose to maintain its work, however, the heart muscle requires an adequate supply of insulin, and of course oxygen. In the diabetic subject, there is failure of utilization of glucose by the heart muscle in a variable degree, but the ability of the heart to consume glucose is restored by insulin. In the normal subject, insulin increases glycogen storage when given in association with glucose, in all muscles and in the liver, but proportionately more in the heart muscle than it does in the skeletal muscles.

In the normal subject, the supply of glycogen in the heart muscle will not be lowered by exercise, provided an adequate supply of oxygen is available. However,

the heart muscle is less tolerant to deprivation of oxygen than is skeletal muscle, and is more sensitive to accumulation of lactic acid. It appears that the formation of glycogen from glucose under the influence of insulin favors the disappearance of lactic acid, thus aiding the recovery of muscle from exercise.

Ingested carbohydrate is absorbed very rapidly. The rise in blood sugar following the absorption of glucose supposedly stimulates the parasympathetic centers in the hypothalamic region of the brain, thus liberating insulin from the pancreas. Hence the beneficial effect noted clinically following the use of a high carbohydrate diet in heart failure may be due to the liberation of insulin in response to the rise in blood sugar, thus enhancing the power of the heart muscle to store glycogen.

#### EFFECT OF INSULIN HYPOGLYCEMIA ON THE CIRCULATION

If insulin is given freely without sufficient glucose, hypoglycemia results. The studies of insulin hypoglycemia effects on the circulation are not all in accord. (2) Increase in pulse rate is the general rule. In some subjects, both the systolic and diastolic blood pressure is lowered, while in others, the systolic level is sustained, or even elevated, and the diastolic level only is lowered. Apparently the decrease is least in the normal subject and greatest in diabetics with hypertension. Ernestene and Altschule (3) report, after study of insulin induced hypoglycemia in 16 normal subjects, an average increase of 29% in the circulatory minute volume, an increase of 73% in the pulse pressure, and an increase of 15% in the pulse rate, thus indicating that hypoglycemia is attended by an increased amount of cardiac work. These changes are similar to those following the use of epinephrine, and animal experimentation indicates that this effect results from stimulation of the sympathetic division of the autonomic nervous system. These signs disappear with the use of glucose in adequate amount.

Electrocardiographic studies during insulin hypoglycemia by various workers (4) have revealed reduction of the amplitude of R and T and in some cases even negativity of T waves, in diabetics with supposedly normal hearts. No clear-cut correlation has been established between the blood sugar level and the degree of change in the electrocardiogram. In patients with myocardial disease, extrasystoles, auricular fibrillation and other changes in rhythm have been demon-

\*Read before The American Therapeutic Society, Cleveland, Ohio, June 1934.  
Submitted December 6, 1934.



strated during insulin hypoglycemia. Middleton and Otway (5) reported three years ago, that after studying 11 diabetics with apparently normal hearts in insulin shock, the most marked change in the electrocardiogram was the flattening or inversion of the T wave.

It is generally agreed that, although the electrocardiographic alterations which appear during insulin shock do not immediately disappear following intravenous glucose injection, yet they are, in a general sense, transitory. Whether these changes are due to hypoglycemia, or due to a direct action of insulin on the myocardium, is not clear. Most continental authors favor the latter idea. Smith, (6) of London, points out that the electrocardiographic changes in *hypoglycemia* are quite similar to the changes to be found in *hyperglycemia*. He believes that in the diabetic, due to deprivation of insulin in the myocardium, there is deficient utilization of glucose, so that defective nutrition of the myocardium results. He assigns a subsidiary role to coronary disease in the diabetic, as far as the production of abnormalities in the electrocardiogram is concerned.

In the treatment of the diabetic with heart disease, occasionally it has been noted that insulin seems to produce angina, and even coronary thrombosis (Parsonnet and Hyman.) (7) In addition, congestive failure may be induced or accelerated through the use of insulin in diabetics with myocardial disease. It is established that anoxemia of the myocardium will give rise to anginal pain; it seems apparent that too extreme a reduction of the glucose supply to the myocardium also will produce anginal pain. Hence it is all the more likely, according to Smith (6), that these two physiological aberrations might cause very similar electrocardiographic changes.

#### SOME EFFECTS OF INSULIN IN NON-DIABETIC SUBJECTS

In more than half of non-diabetic patients with *malnutrition* treated with insulin and high carbohydrate diet, a substantial gain in weight and strength is produced (8). The increase in weight may be due, in part, to the improved appetite following the use of insulin, but it is in part due to the better assimilation of food. It has been noted by almost every physician reporting on the use of insulin in non-diabetic subjects, that insulin exerts a marked tonic effect, in that it increases the feeling of well being in the patient so remarkably.

It has been shown by Boldyreff and Stewart (9), as well as others, that insulin has a secretagogue effect on the gastric glands. Okada (10), *et al* showed that in addition insulin provoked pancreatic and biliary secretions. Leuders and Watson (11) showed that insulin increased the pancreatic ferments in their group of underweight patients under treatment, and improved the character of the biliary secretions in some. Gage (12), *et al* recently have shown that insulin increases intestinal activity. Both experimentally and clinically then, it has been amply shown that insulin improves the function of the entire digestive tract.

Blotner (13) has found, when insulin is used in similar patients, an increase in plasma protein concentration as well as moderate increase in the red blood cells. The same author recently has shown that in some non-diabetic patients there is a slight increase in sugar tolerance following insulin therapy, but con-

cluded the finding was of no practical importance since the tolerance invariably returned to normal later.

#### CLINICAL REPORTS RELATING TO THE USE OF INSULIN-GLUCOSE IN HEART DISORDERS

In 1926 Osato (14) reported one patient with heart failure as being greatly improved by the use of insulin and glucose intravenously. Since then many favorable clinical reports have appeared in the literature concerning insulin-glucose therapy in heart disease.

Rimbaud (15) *et al* used 5 to 10 units of insulin daily or twice daily, with 50 to 100 gms. of dextrose orally, and obtained relief from anginal pain and dyspnoea in their patients. Bickel (16) used from 10 to 30 units of insulin daily, with 100 to 200 gms of dextrose orally or half this amount intravenously. Kisthinos and Gomez (17) claimed good results in patients with heart failure with the use of 4 units of insulin followed by 80 gms of glucose orally for a ten day period.

Jorge and Sobrinhe (18) noted improvement in 10 cases of congestive heart failure, due particularly to right ventricle insufficiency, as evidenced by lessened dyspnoea, diuresis, and lowering of increased venous pressure. They showed electrocardiograms of five patients so treated, demonstrating improved rhythm and in some cases improved amplitude in the ventricular waves. Wiener (19) proclaimed good results but did not state the number of patients treated. Carriere and Hurtz (20) reported in detail their results in 47 patients, using 200 cc of 30% dextrose (60 gms) intravenously, followed by 5 or 10 units of insulin, for a period of ten days. They noted improvement in dyspnoea and precordial distress, slowing of rapid rates, lowering of arterial tension and diuresis in some. In 13 cases, due to exophthalmic goitre, they noted slowing of the pulse rate and disappearance of extrasystoles. Their best results were in patients with congestive heart failure (right ventricle failure) and their poorest results in left ventricle failure without edema. Electrocardiographic studies in some instances showed amelioration of rhythm, disappearance of extrasystoles, but deformities of the ventricular complexes were not influenced by the insulin-glucose therapy. Mathieu, Colleson, and Simonin, (20-a) found favorable changes in the electrocardiograms of ten patients treated with insulin and glucose over a period of one to three weeks. Increased amplitude of R was noted in all, and in two, a flat T became upright.

Amaral (2) reported favorable improvement among 22 patients with heart failure due to valvular lesions, or myocardosis or right failure due to chronic pulmonary disease. He used daily, for ten days, four units of insulin followed by 80 gms of glucose orally.

Lopez-Brenes (22) advocate the use of insulin-glucose in selected cases of myocardial degeneration with coronary sclerosis. They noted in some patients with subjective symptoms without congestive failure, favorable changes in the electrocardiogram, such as disappearance of arborization block.

Sprague and Camp (23) reported in 1932 their results with intravenous glucose without insulin in 12 cases of congestive failure, 3 cases of coronary thrombosis and 4 cases of paroxysmal dyspnoea. The last group only obtained benefit.

Olascoaga (24) states that in 20 patients with cardiac insufficiency of varied etiology, insulin-glucose therapy proved effective even when usual methods

failed. He noted slowing of the pulse rate, improvement in dyspnoea, and disappearance of gallop rhythm and signs of congestive failure. He also depicted with orthodiagrams reduction in size of dilated heart chambers. He found an increase in systolic pressure decrease in diastolic pressure, increase in the oscillographic index, all of which, he felt indicated an improved cardiac tone. If fibrillation of the auricles existed, the results were not so striking.

Recently, Smith and Luten (25) reported their results with intravenous glucose in 16 patients with advanced congestive failure. They concluded such therapy was indicated as an emergency only where digitalis failed to restore compensation and denied insulin any credit. In view of the fact that analysis of their cases reveals that only one patient received more than *three* injections of glucose, while 6 received only *one* injection, it hardly seems worth while judging the efficacy of glucose therapy used so sparingly in the face of a chronic disease process. Furthermore, since they used insulin in only 5 patients, in dosage of 5 units one to three times and 10 units once, it seems obvious that their opportunity to be impressed with the advantages of insulin was meager.

Last year Smith (26), of London, reported quite favorably on the use of insulin-glucose in 40 patients with the anginal syndrome, subject to frequent attacks and preceded by routine therapy without avail. His method consisted of 5 units of insulin twice daily, followed by a meal including 30 gms of glucose, over a period of 2 to 17 weeks.

White (27) in his recent treatise on heart disease makes no mention of the use of insulin and scant reference is made to the use of glucose intravenously. Hyman and Parsonnet (28) in their recent monograph, speaking of therapy in coronary thrombosis recommend highly intravenous glucose in the second and third stages of the coronary attack, but warn against the use of insulin in diabetics, unless the diabetes is severe.

#### INSULIN-GLUCOSE THERAPY IN TWENTY CASES OF HEART DISEASE

This report summarizes my observations on a group of twenty patients with heart disease treated with insulin in association with a high carbohydrate diet, and extra feedings of glucose. The series comprises 13 private cases and 7 from wards of Jackson Memorial Hospital. There were 13 men and 7 women, ranging in ages from 27 to 83 years.

#### METHOD

Patients who received glucose *intravenously*, in association with insulin, were not included in this study. In every instance other drugs either were discontinued, or the patient had a control period of a number of weeks in which to reach a stationary point, before the initial use of insulin-glucose, in order to properly evaluate the insulin-glucose effect. If the patient was in the hospital the nurse was instructed to give five units of insulin fifteen minutes before meals. The diet included abundant carbohydrates, and extra feedings of 30 gms of glucose in fruit juice were given two hours after each meal. If the patient was ambulatory or home under the care of a nurse, he or some responsible member of the household was instructed in the use of insulin. In the event of improvement, the dose of insulin usually was not increased, but if no improvement was noted after a few days, and no intoler-

ance for insulin observed, the dose was then doubled.

Instead of the smaller doses usually advocated, my experience indicates that 15 to 30 units of insulin daily is required to produce maximum benefit. If intolerance for insulin developed, as indicated by nervousness, palpitation, anorexia or nausea, the insulin was discontinued for a few days. If the signs of intolerance developed again on resuming insulin, the method was considered a failure for that patient. The duration of treatment varied from two to eight weeks except in some cases of intolerance.

#### TYPES OF CASE AND RESULTS NOTED

(1) Five patients had suffered previous coronary thrombosis. One had developed congestive failure, and no improvement was noted with insulin-glucose, and she died later. The other four were having angina of effort, or showed signs of left ventricular failure. All of these improved with insulin-glucose, as indicated by lessened dyspnoea, increased strength, or improved tolerance for exercise without angina. The improved spirit in one case was very striking.

This case, Dr. D., was an active surgeon, 48 years of age, who had suffered a coronary thrombosis in April, 1933. On arrival in Miami in January of this year, he could not walk more than a few yards without anginal pain, and was markedly depressed in spirits. By April, he could walk a hundred yards without pain, but the mental state was not much improved. The weight was 122 pounds, fasting blood sugar was 93 mgs. blood pressure was 110/80, examination and electrocardiogram showed nothing remarkable. Insulin was then started, his optimal dose being 30 units daily. He gained ten pounds in weight, felt stronger, tolerance for exercise mounted rapidly, and the effect on the depression was nothing short of remarkable, and I am convinced it was not psychic.

One of these cases used insulin-glucose therapy on several occasions with benefit each time.

C. F., a man of 72 years, has been under observation the past six years. At first he showed only general arteriosclerosis and biliary insufficiency, and insulin was used as a tonic and to induce weight. About two years ago he developed moderate essential hypertension and anginal pain. A year ago he had a coronary thrombosis, for which he was in bed two months. Following this, he developed dyspnoea on exertion, and angina of effort. Insulin was used on three different occasions and each time he improved in strength, and both dyspnoea and anginal pain were ameliorated, and digestion improved. His improved feeling of well-being was notable.

(2) Four patients had coronary sclerosis, combined with hypertension and showed signs of left ventricle failure. One of these, a man of 55, was intolerant to insulin and treatment of usual type was continued. The other three improved moderately, with lessened dyspnoea, slowing of the pulse rate, and increased strength. (The further progress of one was hindered by the onset of pleurisy, after insulin had been used two weeks, but up to that point, improvement was notable.)

(3) Three patients had coronary sclerosis and left ventricle failure, but their clinical picture was overshadowed by a severe chronic nephritis. Temporary amelioration of dyspnoea was noted in these cases, but their disease process soon caused their deaths.

(4) Three patients suffered from angina of effort, and showed evidence of coronary sclerosis without cardiac hypertrophy. All derived definite benefit from insulin-glucose therapy, but did not lose their anginal syndrome completely. One, a man of 83 years, had first been diagnosed angina pectoris 26 years

previously. He was found to have auricular fibrillation also. His clinical picture was clouded, due to a distressful diverticulosis of the colon, and intermittent claudication. His improvement was as much due to his better digestion, probably, as to the effect on the myocardium itself. Another patient, a man of only 34 years, had been told he had a coronary thrombosis, but careful inquiry revealed only a probable coronary sclerosis. There was an element of mild hyperthyroidism in this case, and very likely some severe seizures of precordial pain he developed were of psychogenic origin. At any rate, he gained 27 pounds in six weeks, with the use of insulin-glucose therapy, and made a striking general improvement, and for several months his pains were greatly ameliorated, though since his return north the seizures are intolerable again.

(5) Three patients had mitral stenosis, due to rheumatic heart disease. Two of these were intolerant to insulin (one with tachycardia without congestive failure, and one with marked congestive failure.)

S. M., the patient of this type who did improve, was a man 37 years of age, who gave a history of rheumatic disease in childhood and presented signs of mitral stenosis. There was no evidence of congestive failure, but tachycardia was bothersome, and he was weak and asthenic, his fatigue keeping him abed a great deal of the time. Some foci of infection were eradicated, without any pronounced improvement in his health. He was then given insulin-glucose therapy, with good results. The weight increased 15 pounds, there was much less palpitation, he became stronger and though his progress was interrupted at one time with a severe respiratory infection, he eventually after an aggregate of two months of insulin-glucose therapy, was able to resume his work. He has since maintained his improvement.

(6) Two patients were diagnosed as cardio-neurosis. One of these cases had essential hypertension, and improved in her general feeling of well being and strength. The other showed no improvement after a month's trial with insulin and glucose treatment.

In summary, then, ten, or 50% of the cases showed improvement under treatment with insulin and glucose.

#### ELECTROCARDIOGRAPHIC CHANGES

Electrocardiograms were obtained before insulin-glucose therapy was started in all cases, and repeated at the end of the therapy with some exceptions. In no instance was there any electrocardiographic evidence suggesting that the use of insulin in this fashion had produced unfavorable changes in the myocardium. On the other hand, slowing of rate, disappearance of extrasystoles, increased amplitude of R or elevation of T, was demonstrated in five out of the ten cases who improved with insulin-glucose treatment. This suggests that a beneficial change in the nutrition of the myocardium had been brought about in these cases.

In case O. M., a definite change from negative to upright T-2 occurred, but as this patient had received twelve grains of digitalis during 48 hours prior to the initial electrocardiogram, it is possible that the negative T-2 was in part digitalis effect. In this same case, T-3 had been negative, with high take off, and became isoelectric. Digitalis was withdrawn, and insulin used for only two weeks, then the second electrocardiogram was obtained.

In case C. F., negative T-2 became isoelectric, but in this case insulin was being used for the third time five months after the first electrocardiogram was ob-

tained. It is of course possible the change in T-2 may have occurred in this length of time without benefit of insulin therapy, but even if in each case some reason could be ferreted out to which favorable change might be ascribed other than insulin, the absence of deleterious effect in the electrocardiogram remains significant, and makes one less fearful of such use of insulin.

#### COMMENT

Parkinson (29) has recently reminded us that too much attention has recently been centered on the anginal death, and too little on the anginal life and its management. This applies equally well to most cardiac states, so if insulin-glucose therapy will improve patients with heart disease, and can be used safely, it is worth finding out.

In the many reports in the literature relating to insulin-glucose therapy in non-diabetics, no anginal episodes were recorded, in spite of the occasional report of coronary symptoms following the use of insulin. The fear of insulin reaction in the diabetic with heart disease is justifiable, but in the non-diabetic, partaking of a liberal amount of carbohydrate and extra feeding of glucose, the chance of insulin-hypoglycemia is slim indeed. Those patients I have observed who were intolerant to insulin-glucose therapy, gave notice of their intolerance by palpitation, nervousness, anorexia, and nausea, but not by cardiac pain or collapse. That insulin therapy of this sort may be used with impunity is further borne out in the group studied here, by the absence of unfavorable electrocardiographic changes following the procedure.

If hypoglycemia in the non-diabetic commonly causes cardiac pain, this should be a prominent symptom in the reported cases of hyperinsulinism. But such is not the case, in fact in the symptom complex of 65 cases recently collected from the literature by Tedstrom (30) only one patient had attacks of typical coronary disease. The electrocardiograms on this patient reverted to normal, however, on elevation of the sugar level.

In the diabetic patient, using insulin, the glucose in the diet is calculated to just meet the insulin requirements, so that hypoglycemia is not uncommon. However, in the non-diabetic, such close calculation of diet is not necessary, and an excess of glucose can be given, and should be given, thus avoiding hypoglycemia with its attendant dangers for the cardiac patient, but the "tonic" effect of insulin on the heart is produced, nevertheless.

It is necessary to keep in mind that insulin, (in addition to glucose and oxygen) is required by the heart muscle to do its work. As pointed out above, insulin increases the ability of the heart muscle to utilize glucose, and this effect is directly on the heart muscle, and is not to be confused with the effect of insulin hypoglycemia on the circulation.

Smith (26) is of the opinion that insulin also aids the resolution of early atheromatous changes in the coronary arteries, through promotion of the combustion of fat. He also suggests that the improved nutrition in the myocardium resulting from the use of insulin prevents the accumulation of substances capable of producing anginal pain. In my opinion, although neither of these conceptions can be proved, they have a logical basis on the physiological facts noted above.

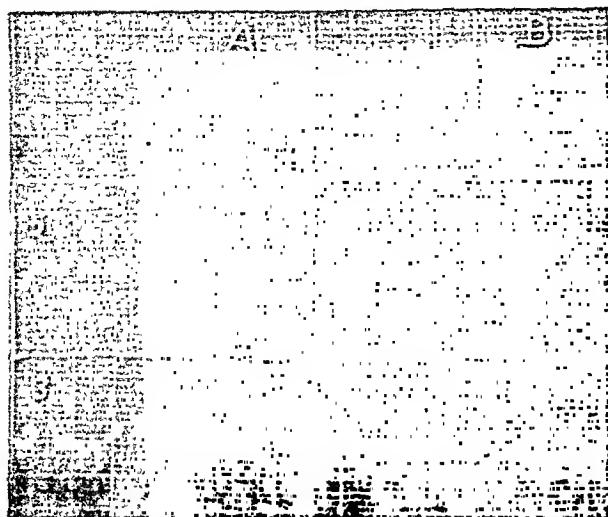


Fig. 1. Case O. M.: Biphasic T-2. Before insulin (A). After insulin-glucose therapy (B). T becomes upright.

Many patients with anginal syndrome have associated gall bladder disease, or other disorders of the digestive tract, which frequently seem to incite the anginal pain. In view of the well established fact that insulin improves the biliary, gastric and pancreatic secretions, it is quite likely that the lessened anginal attacks in some patients, following insulin-glucose therapy, are due to improved digestion. This holds for other types of heart disease also, for the

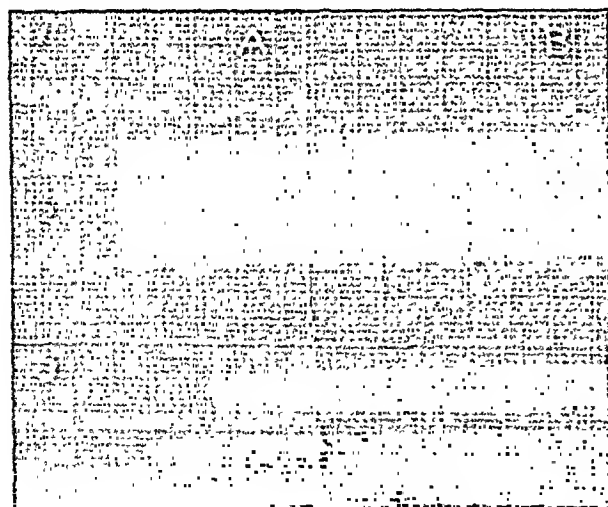


Fig. 3. Case W. A.: Flattened T in all leads and low voltage of QRS before insulin (A). Improved character of T in all leads, increased height of QRS in lead I, with shift to left axis deviation, after insulin-glucose therapy.

flatulence and general abdominal discomfort of many heart patients, particularly those with congestive failure, are important contributing factors hindering their progress, and any improvement in the digestion is a distinct gain to the patient.

I should like to stress the difference between using glucose in the diet, coupled with insulin, as I have done in the 26 cases reported here, and the use of glucose intravenously in hypertonic solutions with in-

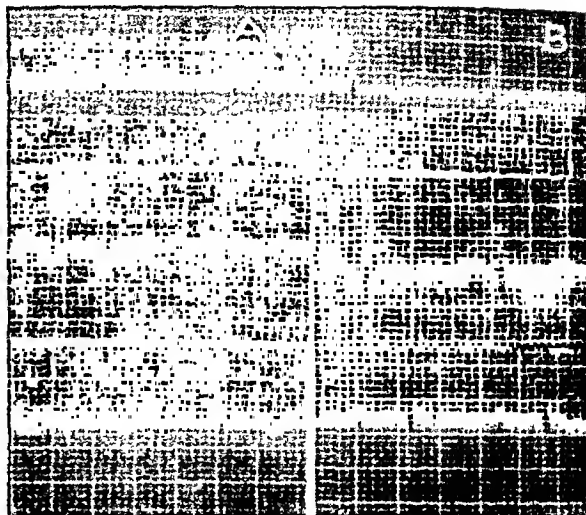


Fig. 2. Case C. F.: Negative T-2 and low voltage of QRS before insulin (A). Isoelectric T-2 and increased height of QRS after insulin-glucose therapy (B).

sulin. The latter method is cumbersome, entails hospitalization, is not without danger, and frequently has to be abandoned because of sclerosis of the veins, and can never be continued many days. On the other hand, by including an ample supply of carbohydrate on the diet, and extra feedings of glucose, insulin-glucose therapy may be continued over as long a time as desired. For example, two patients in this group took insulin for two months. Since insulin improves the

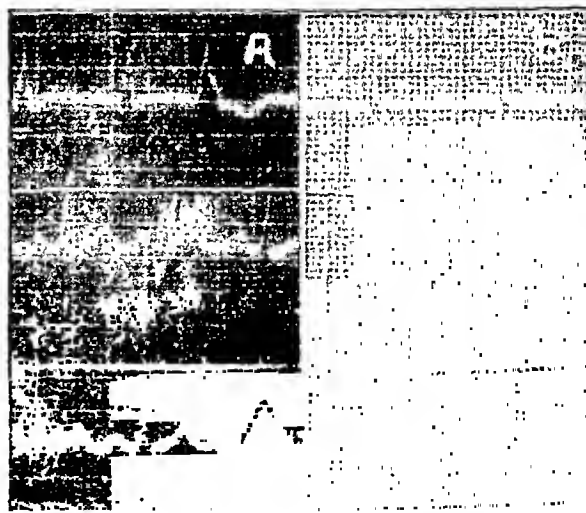


Fig. 4. Case C. K.: T-1 isoelectric, premature contractions present before insulin (A). Decreased height of R but absence of premature contractions after insulin-glucose therapy (B).

digestion, rarely was any complaint registered about the amount of sweet fruit juices necessarily imbibed. There is scant need of using glucose intravenously instead of in the dietary, in the treatment of heart disease, except as an emergency measure in advanced cardiac congestive failure, or in combating shock after coronary thrombosis, or in circulatory shock from other sources.

Probably one of the most important uses of insulin-

glucose therapy will prove to be in the patient with moderate coronary artery disease, without advanced congestive failure. How many patients with myocardial infarction go moping along after their period of acute illness is over, from one to three years, almost afraid to live, their chief preoccupation being the struggle with insurance adjusters! They far too frequently become introverts and arrive at various stages of chronic depression of the spirit. For them, treatment with insulin-glucose serves a double purpose in that it not only improves the actual nutrition state of the myocardium, but through its tonic effect buoy's up the spirit remarkably. And, if by chance they are underweight also, the induced gain in weight has an excellent psychic effect, which may even be reflected from the jovial remarks of their friends.

### SUMMARY AND CONCLUSIONS

The use of insulin, in association with glucose, is not empiric treatment in heart disease, but is based upon physiological evidence that this procedure improves the nutrition of the myocardium.

A review of the numerous published clinical reports

indicates that insulin-glucose therapy has a beneficial effect on various types of heart disease, in spite of the obvious difficulty of assessing the value of any specified treatment in cardiac patients.

In a group of 20 patients with heart disease, 50% improved with the use of insulin in association with a high carbohydrate diet and extra feedings of glucose. Patients with the anginal syndrome or coronary thrombosis, with or without left ventricular failure, are in particular likely to derive benefit from such therapy.

It is not proposed to use insulin-glucose therapy in place of other routine measures, but more as an adjunct to other methods of treatment.

Electrocardiographic studies indicate that no untoward effects are obtained following the use of insulin-glucose in the non-diabetic subject with heart disease, and evidence of improvement in the nutritional state of the myocardium is obtained in some cases.

The benefit derived in cardiac patients is due not only to improved nutrition of the myocardium, but may be due in part to improved digestive functions and elevation of the general spirit of the patient.

### REFERENCES

1. Knowlton, F. P., and Starling, E. H.: Experiments on the Consumption of Sugar in the Normal and Diabetic Heart. *J. Physiol.*, 45:146, 1912.
2. Cruickshank, E. W. H., and Patterson, S. W.: The Sugar Consumption in the Surviving Normal and Diabetic Heart. *J. Physiol.*, 47:381, 1913-14.
3. Patterson, S. W., and Starling, E. H.: The Carbohydrate Metabolism of the Isolated Heart-lung Preparation. *J. Physiol.*, 47:137, 1913-14.
4. Valdes, A.: Glycogen Content of Heart, Liver, and Skeletal Muscle after Death, Following Injections of Glucose and Insulin. *Virechow's Arch. f. path. Anat.*, 274:361, 1929.
5. Bnyliss, L. E.; Mueller, E. A., and Starling, E. H.: The Action of Insulin and Sugar on the Respiratory Quotient and Metabolism of the Heart-lung Preparation. *J. Physiol.*, 65:33, 1928.
6. Long, C. N. H., and Evans, G. T.: Glycogen Content of the Rat Heart. *Proc. Soc. Exper. Biol. and Med.*, 30:186, 1932.
7. Hepburn, J., and Litchford, J. K.: Effect of Insulin on the Sugar Consumption of the Isolated Surviving Rabbit Heart. *Am. J. Physiol.*, 62:177, 1922.
8. Long, C. N. H., and Horsfall, F. L., Jr.: Recovery Process after Exercise in Mammals: Conversion of Infused d-Lactic Acid into Muscle Glycogen. *J. Biol. Chem.*, 95:715, 1932.
9. Best, C. H.: Aspects of Carbohydrate and Fat Metabolism. *Ann. Int. Med.*, 7:145, 1933.
10. Hill, A. V.: Revolution in Muscle Physiology. *Physiol. Rev.*, 12:56, 1932.
11. Fletcher, A. A., and Campbell, W. R.: The Blood Sugar Following Insulin Administration and the Symptom Complex Hypoglycemia. *J. Metab. Research*, 2:637, 1922.
12. Wiechmann, E., and Koch, F.: Untersuchungen über den hypoglykämischen Zustand nach Insulininjektion. III. Das Verhalten des Kreislaufs im hypoglykämischen Zustand. *Deutsches Arch. f. klin. Med.*, 163:176, 1929.
13. Edwards, D. J., and Page, I. H.: Observations on the Circulation During Hypoglycemia from Large Doses of Insulin. *Am. J. Physiol.*, 69:177, 1924.
14. Lyman, R. S.; Nicholls, E., and McCann, W. S.: The Respiratory Exchange and Blood Sugar Curves of Normal and Diabetic Subjects after Epinephrin and Insulin. *J. Pharmacol. & Exper. Therap.*, 21:343, 1923.
15. Weinberger, W., and Heltzman, A.: Does the Pancreatic Hormone (Insulin) Lower the Blood Pressure? Is This Effect Due to Its Action on the Suprarenal Glands? *J. A. M. A.*, 83:1215, 1924.
16. Klemperer, von P., and Strisower, R.: Insulin and Blutdruck. *Wien. Klin. Wochenschr.*, 36:672, 1923.
17. Ernestine, A. C., and Altschule, M. D.: The Effect of Insulin Hypoglycemia on the Circulation. *J. Clin. Investigation*, 10:521, 1931.
18. Wittgenstein, A., and Mendel, B.: Die Veränderung der T-Zacke des Elektrokardiogramms während der Insulinwirkung. *Klin. Wochenschr.*, 3:1119, 1924.
19. Von Haynal, E.: Elektrokardiographische Untersuchungen über Insulinwirkung auf das Herz: II. Mitteilung. *Klin. Wochenschr.*, 4:1729, 1925; also p. 403.
20. Von Haynal, E.; Vidovszky, and Gyorgi, G.: Elektrokardiographische Untersuchungen über Insulinwirkung auf das Herz: III. Mitteilung, Insulin und Geschädigter Herzmuskel. *Klin. Wochenschr.*, 7:1543, 1928.
21. Schaffer, H.; Buckn, E., and Friedlander, K.: Über die Einwirkung des Insulins und der Hypoglykämie auf das menschliche Herz. *Ztschr. f. d. ges. exper. Med.*, 57:35, 1927.
22. Middleton, W. S., and Outway, W. H., Jr.: Insulin Shock and the Myocardium. *Am. J. M. Sc.*, 181:39, 1931.
23. Smith, K. S.: Electrocardiographic Changes During the Treatment of Severe Diabetes. *Lancet*, 1:501, 1932.
24. Parsonett, A. E., and Hyman, A. S.: Insulin Angina: Development of Stenoardial Syndrome Following Administration of Insulin in Diabetics with Coronary Thrombosis. *Ann. Int. Med.*, 4:1247, 1931.
25. Nichol, E. S.: Insulin Fattening: Late Results in Sixty-three Cases. *South M. J.*, 25:405, 1932.
26. Boldyreff, E. B., and Stewart, J. F.: Study of Gastric Secretion Caused by Insulin. *J. Pharmacol. & Exper. Therap.*, 46:375, 1932.
27. Okuda, S.; Kuramochi, K.; Tsukahara, T., and Ooinoue, T.: Pancreatic Function IV. The Humoral Regulation of the Gastric, Pancreatic and Biliary Secretions. *Arch. Int. Med.*, 43:446, 1929.
28. Lueders, C. W., and Watson, M. E.: The Effect of Insulin Therapy on Pancreatic Enzymes in Malnutrition. *Arch. Int. Med.*, 49:330, 1932.
29. Gage, I. M.; Ochsner, A., and Cutting, R. A.: The Influence of Insulin and Glucose on Motility of Normal and Obstructed Intestine. *Arch. Surg.*, 26:539, 1933.
30. Blotner, H.: Observations of the Effect of Insulin in Thin Persons. *J. A. M. A.*, 100:88, 1932; also, Insulin and Sugar Tolerance in Thin People. *Arch. Int. Med.*, 53:153, 1934.
31. Ostro, S.: Effect of Insulin-glucose on Diseased Conditions Other than Diabetes. *Ztschr. f. d. ges. exper. Med.*, 51:488, 1926.
32. Rimbaud, L.; Balmes, A., and Martin, G. A.: L'Association sucre-insuline en thérapeutique cardiaque. *Presse méd.*, 39:1647, 1931.
33. Bickel, G.: L'insuline dans le traitement des affections cardio-vasculaires. *Presse méd.*, 38:1433, 1930.
34. Kisthinos, N., and Gomez, D.: Action thérapeutique du sucre dans l'insuffisance cardiaque. *Presse méd.*, 38:1363, 1930.
35. Jorge, A. L., and Sobrinho, J. P.: Insuffisance cardiaque et l'Association Sucre-insuline. *Presse méd.*, 40:1951, 1932.
36. Wiener, J.: L'insulinotherapie dans les affections cardiaques. *Bruxelles Med.*, 7:188, 1932.
37. Carrière, G., and Huriez, C.: L'Association du glucose et de l'insuline au cours des insuffisances cardiaques. *Gaz. d. Hôp.*, 29:535, 1933.
38. Mathieu, L.; Colleson, L., and Simonin, J.: Recherches électrocardiographiques chez des cardiaques traités par l'association insuline-glucose. *Compt. rend. Soc. d. biol.*, 107:365, 1931.
39. Amaral, F. P. de: A proposito das criticas ao emprego da insulina-glucose-terapia nas cardiopatias e alguns resultados obtidos com a tecnica de Kisthinos e Gomez. *Sao Paulo Med.*, 5:297, 1933.
40. Lopez-Brenes: Tratamiento insulínico en las cardiopatías. *Arch. de Med., cir. y espec.*, 36:521, 1933.
41. Sprague, H. B., and Camp, P. D.: Intravenous Hypertonic Glucose in the Treatment of Cardiac Disease. Preliminary Report. *N. E. J. Med.*, 206:288, 1932.
42. Olaseoaga, J. Q.: Principales acciones fisiológicas de la combinacion azucar-insulina en terapeutica cardiaca. *Arch. latino-am. de cardiologia y hemotologia*, 3:143, 1933.
43. Smith, A. E., and Luten, D.: Study of Glucose Therapy in Heart Failure in Advanced Cardiac Disease. *Am. Heart J.*, 9:437, 1934.
44. Smith, K. S.: Insulin and Glucose in Treatment of Heart Disease, with Especial Reference to Angina Pectoris. *Brit. M. J.*, 1:693, 1933.
45. White, P. D.: Heart Disease. New York City, Macmillan Company, 1932.
46. Hyman, A. S., and Parsonett, A. E.: The Failing Heart of Middle Life. Philadelphia, F. A. Davis Company, 1932, p. 214.
47. Parkinson, J.: Coronary Thrombosis. *Brit. M. J.*, 3741:549, 1932.
48. Tedstrom, M. K.: Hypoglycemia and Hyperinsulinism. *Ann. Int. Med.*, 7:1013, 1934.



# Acid-Base Value and Assimilability of Fruit Juices\*

By

I. NEWTON KUGELMASS, M.D.†  
NEW YORK CITY, NEW YORK

FRUIT juices constitute an essential source of readily available nutrients for sick children. The juices replenish rather rapidly the three body constituents, water, salts and dextrose whose loss even in a small measure markedly affects the regulatory processes of the body. The purpose of the present study is to determine the acid-base values of fruit juices, the gastric response to their ingestion and the degree of availability of their constituents.

## METHODS

The hydrogen ion concentration was determined colorimetrically by solutions standardized potentiometrically. The same fruit juice solutions were used for the determination of total titrable acidity. 100 cc. of some of the fruit juices were offered to convalescing young children as a test meal and the gastric juice obtained by tube at the end of 15 and 30 minutes respectively for their *pH* determinations. Membrane equilibria were studied with 30 cc. of each fruit juice dialyzed in a collodian membrane and suspended in a beaker containing an equal volume of 1% saline solution. The refractive index, the *pH*, the sugar content, the phosphate and the total base all were determined before and after an hour's dialysis for the evaluation of the degree of availability of these constituents.

The *pH* determinations of the fresh fruit juices show that lemon juice has the highest acidity of all fruits, *pH* 2. Orange, grape and pineapple juices have a *pH* value which ranges about 3; tomato, apple and banana juice fluctuate about *pH* 4; beet juice appears on the alkaline side at about *pH* 9. The total titrable acidity parallels the *pH* level of the fruit juices, i.e., the higher the acidity the greater the titration value to *pH* 9. The fruit juices fluctuating about *pH* 3 stimulated with the first 15 minutes after ingestion a gastric *pH* of about 3.5. Fruit juices fluctuating at about *pH* 4 stimulate after a longer period a gastric *pH* of about 4.5. The gastric value obtained upon ingestion of fruit juices apparently depends upon the associated content of the food acid contained—citric in lemon, mallic in apple and the combination of both in tomato. (Table I).

A titration curve of any of the fruit juices reveals that they are mixtures of weak acids and their salts containing relatively small amounts of free acids. Lemon juice, for example, is an acid buffer salt mixture containing about 10% free citric acid, 60% of the primary citrate, 20% of the secondary citrate and about 2% of the tertiary salt. The sugar present in the fruit juices tends to decrease the *pH* value but exerts no buffer value except on the extreme alkaline range beyond biological significance.

These acid-base studies have thus shown fruit juices to be buffer solutions containing sugar. They are rather desirable for administration in the course of acute illness because of the nature of their composition. The question that arises is readiness of the availability of the salts and sugar upon ingestion. A first approach to this problem has been made by setting up a series of semi-permeable membrane experiments with fruit juices in a dialyzing sac and physiologic saline surrounding it. Such an analysis of

TABLE I  
Fruit and Gastric Juice Values

|           | Fruit Juice |                            | Gastric   |
|-----------|-------------|----------------------------|-----------|
|           | <i>pH</i>   | Titrable (H <sup>+</sup> ) | <i>pH</i> |
| Lemon     | 2.2         | 3.9                        | 3.1       |
| Orange    | 3.0         | 1.0                        | 3.6       |
| Grape     | 3.2         |                            | 3.5       |
| Pineapple | 3.4         | 1.0                        | 3.0       |
| Tomato    | 4.2         | 0.5                        | 4.5       |
| Apple     | 4.3         | 0.5                        | 4.8       |
| Banana    | 4.6         | 0.2                        | 4.6       |
| Beet      | 8.8         |                            |           |

relatively simple membrane equilibria *in vitro* is in a physico-chemical sense comparable with the primary conditions which maintain in the upper alimentary tract.

The results given in Table II show that the *pH* before and after equilibrium attainment remains relatively constant in spite of changes in the concentration of the constituents. The refractive index shows the degree of dilution that takes place in the course of exchange. Sugar as a non-electrolyte is the substance that rapidly permeated the membrane. But the basic constituents, the acid or electro-negative ions pass less rapidly than sugar and the basic or electro-positive ions remain more or less intact. In fact, the total base of the fruit juices has been observed to increase in content resulting from the shift of the sodium ion from the dialyzate. While this was at first in discord with the accepted notion of the ready availability of the basic salts in fruit juices, the observation is however in accord with Donnan's theory of membrane equilibria. The inference is that basic salt constituents are the last to be absorbed from such solutions.

The increased basic salt content observed in the distribution of substance on each side of a membrane is due to the presence of a fruit protein, the molecules and anions of which cannot pass through the membrane early in course of digestion. The mechanism of

\*Director of the Institute; Attending Pediatrician to the Broad Street Hospital and Pan American Clinics, the French Hospital, New York; Consulting Pediatrician to the Monmouth Memorial Hospital, the Linn Memorial Hospital, New Jersey.



TABLE II

| Fruit Juice           | pH              |                | Refractive Index (Pulfrich) |                | Sugar gm. 70 cc. |                | Sugar gm %      |                | Total Base (m—Equiv. %) |                | Phosphate (mi—Equiv. %) |                |
|-----------------------|-----------------|----------------|-----------------------------|----------------|------------------|----------------|-----------------|----------------|-------------------------|----------------|-------------------------|----------------|
|                       | Before Dialysis | After Dialysis | Before Dialysis             | After Dialysis | Before Dialysis  | After Dialysis | Before Dialysis | After Dialysis | Before Dialysis         | After Dialysis | Before Dialysis         | After Dialysis |
| Orange juice          | 4.0             | 4.2            | 62.5                        | 48.5           | 3.01             | 1.89           | 4.3%            | 2.7%           | 70.6                    | 93.0           | 22.4                    | 16.8           |
| Lemon juice           | 2.4             | 2.6            | 48.0                        | 36.5           | 1.19             | 0.66           | 1.7%            | 1.0%           | 83.5                    | 125.1          | 20.9                    | 28.1           |
| Grapefruit juice      | 3.6             | 3.8            | 46.5                        | 39.0           | 3.08             | 2.10           | 4.4%            | 3.0%           | 80.5                    | 116.9          | 17.4                    | 15.0           |
| Tomato juice          | 4.2             | 4.3            | 45.0                        | 31.0           | 2.38             | 2.10           | 3.4%            | 3.0%           | 191.6                   | 191.8          | 23.3                    | 17.4           |
| Fresh pineapple juice | 3.5             | 3.5            | 53.0                        | 34.5           | 0.98             | 0.56           | 1.4%            | 0.8%           | 74.6                    | 63.7           | 13.2                    | 5.7            |
| Fresh grape juice     | 4.0             | 4.2            | 97.0                        | 79.5           | 15.05            | 10.50          | 21.5%           | 15.0%          | 62.5                    | 106.0          | 22.2                    | 19.3           |

physico-chemical behaviour may be presented graphically by

|                 |                 |
|-----------------|-----------------|
| Na <sup>+</sup> | Na <sup>+</sup> |
| R —             | C <sub>1</sub>  |
| I               | II              |

The NaCl diffuses from II into I until an equilibrium state is reached, presented by

|                  |                  |
|------------------|------------------|
| Na <sup>+</sup>  | Na <sup>+</sup>  |
| R —              |                  |
| C <sub>1</sub> — | C <sub>1</sub> — |
| I                | II               |

Donnan formulated mathematically the reason for this change in concentration which can be represented in the initial and equilibrium states as follows:

#### Initial State

|                 |                |                 |                  |
|-----------------|----------------|-----------------|------------------|
| Na <sup>+</sup> | R—             | Na <sup>+</sup> | C <sub>1</sub> — |
| C <sub>1</sub>  | C <sub>1</sub> | C <sub>2</sub>  | C <sub>2</sub>   |
| I               |                | II              |                  |

#### Equilibrium State

|                     |                |                  |                     |                     |
|---------------------|----------------|------------------|---------------------|---------------------|
| Na <sup>+</sup>     | R—             | C <sub>1</sub> — | Na <sup>+</sup>     | C <sub>1</sub> —    |
| (C <sub>1</sub> —X) | C <sub>1</sub> | X                | (C <sub>2</sub> —X) | (C <sub>2</sub> —X) |
| I                   |                |                  | II                  |                     |

This is the nature of things observed in the dialyses of the fruit juices which has definite bearing upon assimilability of the fruit juice constituents by the living membranes of the alimentary tract.

#### CONCLUSIONS

1. Fruit juices are buffer salt solutions whose utilization is favored by their acidity.
2. The dissolved sugar in fruit juices is the most readily absorbed constituent.
3. The fruit juices whose *pH* ranges at about 3—lemon, orange, grape and pineapple create a higher gastric content than those whose *pH* range fluctuates at about 4—tomato, banana.
4. The base-forming constituents of fruit juices are the slowest to be absorbed by virtue of the existent Donnan membrane equilibria.

## A New Concept of Meniere's Disease and its Response to Antiretentional Therapy

By

EUGENE FOLDES, M.D.\*  
NEW YORK CITY, NEW YORK

**R**ETENTION of water, salt and other mineral substances in one organ or another, frequently is productive of disease. The diseases developed in this manner are usually classified under various headings. Thus, temporary intracranial accumulation of liquids appears to play a most significant role in the patho-

genesis of epilepsy and migraine, customarily grouped with the diseases of the nervous system. Similarly, eclampsia of pregnancy, attributed to toxemia of pregnancy, would seem rather to be due to temporary intracranial accumulation of liquids. The same factor appears to be pathogenically important in eclampsia of infancy, frequently brought into relationship with spasmophilia. Aside from the brain, temporary liquid retention also may occur in other organs. Under certain conditions angina pectoris ("coronary disease") may develop if temporary accumulation of liquids

†All the foregoing considerations have been made the subject matter of a monograph (Foldes, A New Approach to Dietetic Therapy, etc. Metabolism of Water and Minerals and its Disturbances, Richard G. Badger, Boston, 1933) to which I refer for detailed description and bibliography.

\*Formerly Assistant Professor of Medicine, Univ. of Budapest, Hungary. Submitted February 9, 1935.

takes place within the pericardium, bronchial asthma ("disease of the lungs") if it develops in the lungs, gout ("disturbance of the uric acid metabolism") if in the joints, allergic diseases if in the mucous membranes of the respiratory organs, of the gastrointestinal tract, or in the skin, etc. All these diseases manifest themselves in the form of attacks of one kind or another, and in all of them the accumulation of liquids is temporary in the organ of pathogenic significance and occurs simultaneously with the paroxysm. The elimination of such temporary retentions would seem to bring the attack to an end. Attention is called to the fact that although all these attacks seem to be directly due to a liquid accumulation which is local in its extent, nevertheless in all conditions enumerated there is also a generalized liquid retention present throughout the organism. In other conditions the generalized retention of liquids in itself, which is permanent rather than temporary and has no local predilection, appears to be pathogenically significant, as for instance in hypertension, pernicious anemia, etc.†

With reference to the diseases characterized by paroxysms and caused (in addition to other factors) by a temporary and local retention of water and minerals, I have called attention to the fact the *Menière's disease* (the term preferred by otolaryngologists is *Menière's syndrome*) seems to belong with this group. Thus, according to Wittmarck (2), *Menière's disease*, consisting of sudden paroxysms of dizziness which are associated with nausea, vomiting and unilateral deafness and tinnitus, is due to the sudden increase of the endolabyrinthial pressure caused by temporary accumulation of liquids within the labyrinth. Wittmarck assumes that the disturbances in the function of the vestibular apparatus are caused by a paralysis of the terminal parts of the sensory nerve and organ due to the increased pressure. In favor of this assumption he calls attention to the fact that after the attack, the disturbance in function disappears to a great extent. In severe cases, degenerative changes of an irreparable character develop as a consequence of hydrops. Further, Dederding (3) finds that there is a relationship between the water and mineral metabolism and *Menière's disease*, inasmuch as there is a relapse following water retention and an improvement after increased diuresis produced by the administration of salyrgan. This author assumes that *Menière's disease* develops on the basis of an edema of the labyrinth.

Accordingly, there seems to be a striking similarity in the pathogenesis of *Menière's disease* on the one hand, and on the other of epilepsy, eclampsia of pregnancy, eclampsia of infancy, migraine, angina pectoris, bronchial asthma, the allergic diseases and gout. All these diseases manifest themselves in the form of attacks which appear to be due to a retention of water and minerals that is (1) local and (2) temporary, rather than generalized and continuous. Also, in all of these diseases, the attacks cease when the retained liquids disappear from the respective organ. The fact that notwithstanding these similarities, the affections enumerated appear to be so widely different that most of them were grouped with the diseases of the various organs rather than with the disturbances of the water and mineral metabolism, is attributable to the difference in the location of the liquid retention, inasmuch as it occurs in one or the other of the various organs.

The characteristics of the organ entering the clinical picture and modifying it to a great extent, and the lack of recognition of the underlying factor of the disturbed water and mineral metabolism in every instance, explain why the analogies escaped attention for a long time.

For the treatment of the group of diseases under discussion an antiretentional therapy has been developed. This therapy is based on the consideration that if retention of liquids plays such a significant—*sine qua non*—rôle in pathogenesis as has been assumed, elimination of retained liquids and prevention of subsequent development of retentions should prevent the occurrence of the paroxysms enumerated. For this purpose, the antiretentional therapy employs a diet, based on the recognition of the fact that all food elements, such as proteins, carbohydrates, fats, water, minerals and vitamins influence the water and mineral metabolism in one direction or the other, i.e. leading either to retention or increased diuresis. Restricting the amount of food elements in the diet which are retentive and utilizing in a liberal measure those of antiretentional properties, the antiretentional diet is built in the following manner.

*Proteins* (antiretentional) are administered in liberal amounts, 1.5 to 1.8 grams per kilogram ideal weight, daily.

*Carbohydrates* (retentive) are restricted to 2.5 to 3.5 grams per kilogram ideal weight daily in the initial stages of the therapy and later increased to the extent which is necessary to maintain the body weight.

*Fats* (retentive) are restricted to from 40 to 50 grams daily.

*Minerals*: Excess in the ingestion of salt (retentive) is to be avoided (in certain cases an unsalted—not salt-free—diet is administered). Other mineral substances are to be employed only as represented in the various food substances.

*Liquids* (frequently retentive) are restricted to from 1.0 to 1.5 liters daily including the liquid content of fruits.

*Vitamins* (mostly antiretentional) are freely utilized but only in their natural state (concentrated preparations are given only in case of special indication, and only occasionally and in small amounts).

The antiretentional diet has been put to a test in such conditions as were attributed to liquid retention, local and temporary, as well as generalized and continuous. The results were gratifying in most instances. In view of the fact that the pathogenesis of *Menière's disease*—with reference to which no therapeutic attempts have been described in the previous publication because no suitable cases were encountered before the work was closed—seems to be essentially similar to that of the other diseases in this group, and differs only as to the location of liquid retention, it was proper to examine the effects of the new therapy upon it.

I found that while the antiretentional diet in itself, or together with the administration of phenobarbital, is ineffective, the addition of quinine sulphate, phenobarbital and the extract of *nux vomica* to an antiretentional diet, the protein content of which is slightly lowered (to approximately 1 gr. of protein per kilogram ideal weight daily) is followed by a complete

disappearance of the attacks within a few days, with no relapses observed thus far.

*The diet administered was as follows:*

*Breakfast:* 180 cc. orange juice, from 30 to 60 grams of bread, one square of butter, one cup of coffee (cafein extracted), one tablespoonful of cream, one teaspoonful of sugar.

*Lunch:* 30 grams of cheese, or two eggs, raw vegetables such as lettuce and tomatoes, 30 to 60 grams of bread, 150 to 180 grams of raw fruits.

*Dinner:* 120 to 150 grams of meats, calf's liver, chicken or fish, vegetables (using those, the carbohydrate content of which does not exceed 17 per cent,) 30 to 60 grams of bread, 150 to 180 grams of raw fruits.

Over twenty-four hours, 4 glasses of water.

*The medication administered was the following:*

Quinine sulphate 0.25 gm.

Phenobarbital 0.02 gm.

Extractum nucis vomicae 0.01 gm.

This was given three times a day for two weeks, then twice the day following, once the next day and, after an interval of three days, the same medication was repeated in a similar manner for the same period. Subsequently the diet as well as the medication was discontinued.

#### CASE REPORTS

1.—*Mr. J. D., age 43.* One niece is suffering from headaches, no other family history. Complains of terrific dizzy spells. Fatigued in the morning of the day of the attacks, in addition to which later belching, heaviness in the stomach and headaches on both sides of the forehead develop until he is seized by sudden dizziness, nausea and usually vomiting. The attacks last several hours, during which time he has to maintain a reclining position. The first such paroxysm occurred fifteen years ago, the second, ten years ago, during the last two years they developed at irregular intervals from once weekly to once in two or three months, while during the last two months they occur on the average of once a week. For the past eight years he has eschewed meats and taken ten glasses of water daily. All previous examinations gave negative results and all forms of treatment were ineffective.

The examinations showed a deafness of the right ear, lateral nystagmus and bradycardia (pulse rate 56), but no other changes.

After the beginning of the therapy (September 6, 1932) the dizzy attacks did not again recur. In the first few days, occasional headaches of short duration and heaviness in the head manifested themselves, but subsequently even these disappeared. Four days following the discontinuance of the therapy, the patient experienced an attack of headache, vomiting and perspiration without dizziness, but since has enjoyed complete freedom from attacks to date (January, 1935).

2.—*Mrs. I. M., age 46.* Ten years ago tinnitus of the left ear for more than a year. Tinnitus of the same ear six years ago for a month. For the past two months severe spells of dizziness almost daily forcing her to maintain a reclining position. Dizziness also on moving the head and on changing position.

The examinations showed deficient hearing bilaterally, but no other changes.

On the first day of the therapy (February 28, 1933) the patient had an extremely severe attack of headache with polyuria, but the dizzy spells disappeared within a few days and have not recurred to date (January, 1935). Dizziness was experienced only on changing position for a few weeks after the beginning of the therapy and occasionally thereafter.

3.—*Miss I. M., age 46.* For the past four weeks, two or

three times weekly spells of dizziness, ringing in the right ear and nausea, forcing her to lie down.

Except for defective hearing of the right ear, the examinations were negative.

On the second day of the therapy (September 12, 1933), a very severe attack of dizziness occurred after which the symptoms did not recur (last heard from June, 1934).

4.—*Mr. S. S., age 38.* For the past four years ringing in the right ear. For the past two years attacks of severe dizziness for about two hours, followed by vomiting for from seven to eight hours. Before the attacks there is a gradual increase of the tinnitus, and following them a decrease. Feels weak and has no appetite for a day or two after the paroxysms. These formerly occurred once in three to four months, for the past three months, however, twice weekly. All previous examinations revealed normal conditions aside from a unilateral impaired hearing, and patient was discharged with the explanation that no effective therapy existed (New York Hospital).

The examination showed a defective hearing of the right ear, but otherwise conditions were essentially normal.

Following the beginning of the therapy (September 7, 1934) a polyuria developed on the second and third day and a mild headache on the fourth day; felt dizzy and had aura several times for a few minutes. Yet, the dizzy spells and vomiting did not recur (last information May 1, 1935).

#### COMMENT

In an attempt to analyze the mechanism of the effect of the therapy outlined, attention is called to the fact that the antiretentional diet, either by itself or in combination with the administration of phenobarbital, was ineffective. On the other hand such a complete abolition of the attacks as has been observed in these four cases can hardly be ascribed to the medication in itself. I shall endeavor to show that the therapeutic results might be explained assuming a concerted action of the diet and medication.

As to one constituent of the mixture consisting of quinine sulphate, phenobarbital and extract of nux vomica, phenobarbital was found to be ineffective in a case (Mr. J. D.) in which the addition of the other two constituents, in combination with the diet, led to a cessation of the paroxysms. Nevertheless phenobarbital was retained for the reason that it apparently has a stabilizing effect on the water metabolism which in Menière's disease seems to be disturbed. It has been pointed out, that phenobarbital has diuretic effects in certain instances of liquid retention, and in other instances is capable of preventing sudden mobilization. I have called attention to the fact that in that group of diseases to which Menière's disease also belongs, both retention and mobilization of liquids are undesirable from a therapeutic point of view.

Further, it is not likely that the administration of the extract of nux vomica by itself could have produced the improvement in the cases described. Yet it was included in the mixture for its well known tonic effect on the nervous system, with the hope that the vestibular nerve might thus be influenced.

Although conclusive evidence is yet to be obtained, it may be assumed that the really potent factor of the mixture is quinine sulphate which, according to some observers, occasionally brings relief from the horrors of Menière's disease. The fact that the great majority of investigators could not confirm the favorable results, however, and that for this reason it is but rarely employed today, demonstrates sufficiently that the results observed in the four cases previously described are not attributable to the administration of quinine

sulphate by itself, but to the concerted action of quinine sulphate and the diet. Such concerted action might be assumed for the following reasons.

Menière's disease may be recognized as apparently a member of the group of pathological conditions caused by temporary local liquid retention. Consequently the absence of therapeutic response of Menière's disease to the antiretentional diet which has shown its effectiveness in a considerable number of various cases, had to be attributed to an unusually firm fixation of liquids in the organism affected by this disease. With respect to conditions with manifest edemas, occasionally the apparently paradoxical phenomenon can be observed that a lively diuresis sets in with partial or total disappearance of the edemas, if the retentions are temporarily increased by the sudden introduction of considerable amounts of water (Volhard's "Wasserstoss"). In an attempt to utilize this phenomenon and in the expectation that the antiretentional effects of the diet might manifest themselves if the retentions in Menière's disease are temporarily increased, the administration of quinine sulphate was chosen, Averbuck (5) having shown that it causes a significant liquid retention in the animal organism. Furthermore, the amount of the diuretically effective proteins administered in the diet was reduced below the level usually employed in antiretentional therapy in order to facilitate the development of such a temporary augmentation of the liquid retention. This was done in the expectation that, after the increased retention brought about by the administration of quinine sulphate and facilitated by the dietary measure of reduced administration of proteins developed, the still powerful antiretentional effects of a diet restricted in carbohydrates, fats and liquids would be sufficient to provide for the necessary diuresis.\* In fact, attacks of dizziness and headaches were observed on one of the first days of the therapy in all four cases, a manifestation of sudden increased liquid retention in the labyrinth and intracranially. A considerable polyuria was also reported by some of the patients, apparently a manifestation of elimination of retained liquids.

These occurrences, as well as the uniformly complete results obtained by a therapy designed as antiretentional, favor the assumption that Menière's disease, similar to the other pathological conditions of the group (epilepsy, etc.), develops on the basis of a disturbed water and mineral metabolism. In addition to this factor, however, it is necessary to postulate a local predisposing factor in the labyrinth, such as a local disturbance of the circulation therein. Attention should be called to the fact that it is necessary to postulate such a factor in certain cases of epilepsy, migraine, angina pectoris, etc., as well. Without this postulate the affection of only one ear could not be explained in Menière's disease.

If the view is accepted that Menière's disease develops on the basis of a disturbed water and mineral metabolism and a local unilateral circulatory disturbance in the ear, the following picture of the pathogenesis can be drawn. Under the influence of intrinsic factors, such as the endocrine system, gastric function, etc., or under the influence of extrinsic factors, such as the diet, atmospheric conditions, etc., liquid retention may develop. These retained liquids are

distributed over the entire organism, and the water content enclosed in both labyrinths also increases to a certain extent. If in addition to such an augmentation of the liquid content of the labyrinth as is due to the general retention, there is a further increase on one side due to a local predisposition (disturbed circulation), the endolabyrinthial pressure may increase to a level where the functions of the terminal parts of the nerve and sensory organ are affected, and dizziness develops. Furthermore, similar to the "mobilizational type" of attacks in epilepsy, migraine, angina pectoris, allergic diseases, gout, etc., it is also possible that in Menière's disease such local liquid retention may develop not when the retentions throughout the body are on the increase, but rather at precisely that time when the liquids accumulated in distant parts of the body become suddenly mobilized and start circulating. Part of these liquids would seem to pass through such parts of the body where there are no barriers, and they would thus seem to be eventually eliminated by the kidneys. In the labyrinth of the one ear, however, where, as postulated, a local circulatory disturbance exists, part of the liquid may be temporarily retained and lead to an attack. Both in this (mobilizational) type of attack as in that previously described which may be termed "retentional," the paroxysm would seem to come to an end when the locally retained liquids are released. These may then either be retained in other parts of the body where they manifest themselves in the form of other symptoms (headache, etc.), or be ultimately eliminated by the kidneys.

Since there are no available data as to the state of the general water and mineral metabolism in Menière's disease, it cannot yet be determined whether only the retentional or the mobilizational type or both may occur and, if the latter is the case, which type is the more frequent. From the fact observed by Dandy (6), however, that in only one of forty-two cases was there an intense desire to urinate during the attack, it seemingly follows that the mobilizational type is not the more frequent. Obviously the polyuria in this case might have been a result of the sudden mobilization of liquids.

On the basis of this concept of Menière's disease, the nausea and vomiting accompanying the dizzy attack may either be due to a so called reflex irritation, or to a simultaneous intracranial liquid accumulation. The frequency of complaints with reference to headaches independently of the dizzy spells in Menière's disease favor the latter assumption.

Menière's disease has been identified in the foregoing as belonging to that group of diseases which includes epilepsy, eclampsia of pregnancy, etc. However, in one respect it occupies a special position among these pathological conditions, i.e., while in epilepsy, migraine, angina pectoris, etc., there is usually a relapse within a few weeks after the antiretentional therapy is discontinued, in Menière's disease no relapse has been observed so far (longest observation over two years), although, as indicated, all antiretentional therapy was discontinued after approximately one month. This occurrence perhaps could be explained by assuming the existence of a vicious circle in the pathogenesis of Menière's disease, the development of which would be made possible by the presence of (1) a local lesion in the labyrinth and (2) a general disturbance of the water and mineral metabolism.

\*In other diseases of the group, the members of which have been previously enumerated and in which therapeutic results are to be had without such temporary augmentation of retentions, the antiretentional effects of larger amounts of proteins should be utilized.

The links of this vicious circle appear to be the following:

Local accumulation of liquids in the labyrinth due to generalized water and mineral retention and local circulatory disturbance—additional impairment of the local circulation due to posthydropic changes—further local liquid retention, etc. Through antiretentional therapy, as suggested, this vicious circle seems to be broken and the subsequent development of attacks thus prevented.

#### SUMMARY

A theory of the pathogenesis of Menière's disease and a therapy based on this concept is offered for further investigation and control. While the number of cases observed (four) is small, the complete disappearance of the attacks in all cases, with no relapses, is noteworthy. The significance of this observation is illustrated by the fact that, according to Dandy (6), "until the advent of sectioning of the auditory nerve there was no treatment, either curative or palliative, of Menière's disease that is worthy of mention."

#### CONCLUSIONS

1. Menière's disease seems to be caused by temporary local accumulation of liquids (in the labyrinth). Thus Menière's disease seems to belong in the group of diseases comprised by epilepsy, eclampsia of pregnancy, eclampsia of infancy, migraine, angina pectoris, bronchial asthma, allergic diseases, gout, etc.

2. Antiretentional therapy consisting of a diet and the administration of quinine sulphate, phenobarbital and extractum nucis vomicae was followed by cessation of the attacks in all (four) cases observed.

#### REFERENCES

1. Földes: A New Approach to Dietetic Therapy, etc., Metabolism of Water and Minerals and Its Disturbances. Richard G. Badger. Boston, 1933.
2. Wittmarck, in Bergmann and Staehelin, Handbuch der inneren Medizin V (1), Berlin, 1925.
3. Dederding: Clin. Exp. Exam. in Patients Suffering From Mb. Menière, 1, Helsingfors, 1929.
4. Földes: A New Aspect of Migraine, etc. Amer. Journ. Digest. Dis. and Nutrit., 1:359, 1934.
5. Averbuck, Naunyn: Schmiedeberg's Archiv., 157:330, 1930.
6. Dandy: Arch. of Otolaryngol., 20:1, 1934.

## ABSTRACTS

DR. K. UEBLEISEN.

*Dietetic Treatment of Chronic Gastritis. Therapie d. Gegenwart, June, 1934.*

The etiology of gastritis is manifold and the diagnosis of gastritis should be made only by careful exclusion of other pathology. He claims that irrespective of the amount of acids, or of increased motility, the important factor remains to put the glandular apparatus to rest. This is accomplished by repeated administration of weak teas, freshly prepared fruit juices, gruels, and the application of cataplasms upon the stomach. Hyper-acid cases clear up rapidly manifested by subsidence of hypersecretion, spasms and amelioration of pains. Salt free and lacto-vegetarian diet is very useful in these cases and sub and anacid varieties also respond favorably. In emaciated patients proper doses of insulin may help to restore the weakened function of the glandular apparatus. When dealing with true inflammatory gastritis of a more severe degree, rest in bed with an initial starvation is prescribed. In weak individuals hypodermoclysis with or without food is administered. Two or three days later the above prescribed diet is instituted gradually turning to light diets consisting of cakes and zwieback and compottes. Gastritis accompanied by abundant secretion of mucus responds favorably by a lavage before retiring. Later the partaking of alkaline waters is advisable. The diet continues to be scarce in sodium chloride and one may add purees, butter eggs, jellies, brains, sweet-breads, juices of vegetables, and salads. Milk is given only after the salt free diet has achieved its desired results. Then some salt may be given. Animal proteins are offered at first as fish. Naturally there are no condiments given. Such a salt free and non-irritating diet is followed by good results especially in achylic gastritis, where the tenacious gastrogenous diarrheas are often favorably influenced. To counteract such diarrheas, other procedures, the administration of calcium salts and jellies or a new apple diet should be

tried. The author gives one pound of grated apples five times a day, carefully eliminating the seeds and he claims results in two or three days. The effect is due supposedly to the tannic acid content.

M. E. Gabor, Milwaukee.

CUTTING, REGINALD A., M.D., C.M., Ph.D.

*Absorption of Dextrose and Water by the Small Intestine and Colon. Arch. Surg., Vol. 29, No. 4, Oct., 1934, pp. 643-661.*

This article presents a review of the literature and a series of experiments as carried out in dogs on the absorption of dextrose and water from the small intestine and colon.

The opinion that dextrose is absorbed only slightly, if at all, by the colon does not seem to be supported by experimental evidence.

Hypertonic sugar solutions in the rectum cause water to be withdrawn from the intestine and this increase in bulk stimulates expulsive movement. It has been shown that actually less dextrose is absorbed from the lower part of the intestinal tract from a ten per cent dextrose or hypertonic solution than will be absorbed from an isotonic or five per cent dextrose solution. Hypertonic solutions interfere actively with the absorption of water as well.

Although the author feels that according to these experiments the lower portion of the intestinal tract under favorable conditions is capable of absorbing considerable quantities of dextrose and water and although proctoclysis can, therefore, be regarded as of definite clinical value, the amount of absorption of dextrose which occurs low in the intestinal tract is only a fraction of that which occurs in the jejunum. Rectal administration of dextrose is therefore only a relatively inefficient substitute for oral administration, and should be adopted only when for one reason or another oral administration is contraindicated.

N. W. Swinton, Boston.

## SECTION IV—Roentgenology

### Carcinoma of the Body of the Pancreas: A Clinico-Roentgenologic Diagnosis\*

By

MARTIN G. VORHAUS, M.D.  
NEW YORK CITY, NEW YORK

**T**HERE are many obscure clinical syndromes still awaiting recognition. Too many of these require post mortem study for their identification. However, not uncommonly, the clinician can arrive at an accurate concept of many of them by a close correlation of the clinical findings and the abnormalities revealed radiographically. This report is an illustration of the dove-tailing of such data.

Carcinoma of the pancreas is relatively uncommon. The incidence is given as 1.5% of all carcinomata (1). Its clinical recognition long has been delayed. Pathological studies show that the pancreas is the site of secondary invasion of carcinoma more frequently than it is the origin of a primary growth (2).

In the past few decades, many reports have appeared of the recognition of carcinoma of the head of the pancreas. This is the most likely location for a primary pancreatic carcinoma and occurs in 66-2/3% of all such pancreatic neoplasms found surgically (3). Autopsy statistics place its occurrence at the higher figure of 80% (4). It is not the greater frequency alone which has made carcinoma of the head of the pancreas a disease which is diagnosed often. The close relationship of the second portion of the duodenum and the common bile duct to the head has afforded tell-tale information.

It is accepted now that this disease should be suspected in a case of painless, deepening jaundice, usually in association with a small, firm liver and often, but not always, accompanied by an enlarged gall bladder. To these clinical facts is added the roentgen demonstration of an increased convexity of the second portion of the duodenum, to the right, producing a capital "C" configuration, and usually revealing a delay in the barium transit through this region. The dove-tailing of these clinical and roentgen findings have led many—and should lead more—to the early recognition of primary carcinoma of the head of the pancreas.

The pancreas apart from its head, is more rarely involved. Occasionally, the tail alone is the site of primary carcinoma; its recognition is extremely difficult. One observer (1, 5), reported only three such cases, seen in twenty-five years of search. Each of these gave the confusing roentgen findings of a large,

irregular, "infiltrating-like" lesion on the greater curvature of the stomach in the medio-gastric region, the shadow of which most closely resembled a gastric carcinoma. Operation and autopsy disclosed a primary carcinoma of the tail of the pancreas. The roentgen defect in the stomach was due to attachment or extension to this organ from the primary lesion.

The sole remaining site for carcinoma of the pancreas is its body, or mid-portion. A complete review of the literature reveals some reports (6, 7, 8, 9, 10, 11) upon the pathologic findings and suggestive clinical data. Several roentgen articles (12, 13, 14), in discussing the findings in carcinoma of the head of the pancreas and in pancreatic cyst, state that carcinoma of the body of the pancreas should show roentgen changes in the duodenum. However, this Author could not find a single report of the clinical and roentgen findings which would enable such diagnosis to be established. For that reason, this case is reported.

#### CASE REPORT

S. H., 59 year old male, admitted to the Medical Service on October 25, 1934, complaining of pain in the back, in the region of the lower thoracic vertebrae.

On August 11, 1934, he had been hospitalized in Brooklyn for the same complaint. He stated that he had had this pain for from four to five months. It was relieved by aspirin, associated disturbances were epigastric pain, constipation and a weight loss of twenty-five pounds during the preceding five months. The examination at the previous hospital (which included, in addition to the usual clinical and laboratory studies, roentgen films of the spine, the gastro-intestinal tract and the gall bladder), failed to reveal any positive anomalies; he was discharged on September 18, 1934, "with no positive findings and, in all probability was suffering with a myositis."

On admission here, the patient complained of a dull, nagging pain in the back, located in the region of the lower thoracic and upper lumbar vertebrae. The pain practically always was present; at times was severe, radiated up and down along the spine for short distances, but did not radiate anteriorly. Several months after the onset of the back pain, the patient stated that he experienced the same type of pain in the epigastrium and that this radiated straight through to the back pain; it was more severe when the back pain was increased. Both pains were greatly aggravated by walking but bore no relation to coughing, breathing, defecation or urination and little, if any, relation to food. Since discharge from the other hospital, he had lost more weight, the total loss being fifty

\*From the Medical Service of Dr. Albert A. Epstein, Hospital for Joint Diseases.  
Submitted February 9, 1935.





Fig. 1

pounds since the beginning of his illness. His weight, on admission, was 100½ pounds. Marked constipation was present. In addition, he complained of anorexia, increasing weakness and insomnia due to pain. There was nothing of significance in his past or in his family history. Syphilis was denied by name and signs.

The *physical examination* revealed a markedly emaciated, elderly, white male who, although weak, was oriented and cooperative. The head and neck revealed no significant findings except for a thickly coated tongue and dry lips. The fundi showed moderate arterio-sclerotic changes. The cardiovascular system showed moderate arteriosclerotic changes although the heart was enlarged only slightly, and the blood pressure was 126/90. The lungs were negative except for some dullness at the left apex and some harsh breathing at this point.

The *abdomen* was scaphoid and tense. There was some tenderness, on deep palpation in the epigastrium but no mass was palpable. The liver was enlarged from one to two fingers' breadth below the costal margin and the edge was smooth and firm. No other abnormalities were present in the abdomen. There was slight tenderness, posteriorly, over the eighth, ninth and tenth dorsal vertebrae and at the costo-vertebral angles. The remainder of the examination revealed nothing of significance.

The *clinical impression* was that of unidentified malignancy and a diagnostic survey was instituted. The neurologist (Dr. Rosenheck), expressed the opinion that there was no primary neurological condition to account for the pain. The urine revealed nothing of significance. Fractional gastric analysis gave figures within normal limits.

Fig. 1. Immediate Film.

The blood counts ranged from 75 to 90% hemoglobin, 4.6 to 5.3 million r. b. c., 10 to 16 thousand w. b. c., with a relatively normal differential count. Serological tests were negative, as was the blood chemistry.

*X-ray of the chest* showed only a thickened pleura at the left apex and some increased sclerosis of the aortic arch. X-ray of the lumbosacral spine and pelvis disclosed no definite evidence of a metastatic neoplastic process. There was a sacralization of the fifth lumbar vertebrae on the left side with moderate arthritic changes in the vertebral segments. (Dr. Pomeranz).

*X-ray of the gastro-intestinal tract* gave the first real clue to the diagnosis. There was no apparent intrinsic disease of the stomach (Fig. 1). There was increased peristalsis with a tendency towards segmentation. A dotted line has been drawn on the film to show the probable outline of the greater curvature of the antrum. The duodenal cap is moderately dilated and shows no defects. The descending portion and the beginning of the transverse portion of the duodenum are markedly dilated. To the left of the third lumbar vertebrae can be seen a well filled duodenal-jejunal junction which appears normal. Figure 2 is a three hour observation and shows that the stomach is almost completely empty. There is a mass of barium located at the level of the third and fourth lumbar vertebrae, slightly to the right of the mid-line, which seems to be in the duodenum. This is more apparent in the six hour film (Fig. 3), at which time the descending portion and beginning of the transverse portion of the duodenum are seen clearly, filled with barium and slightly dilated. The descending portion of the duodenum shows no loss of its normal markings, and its configuration and position are

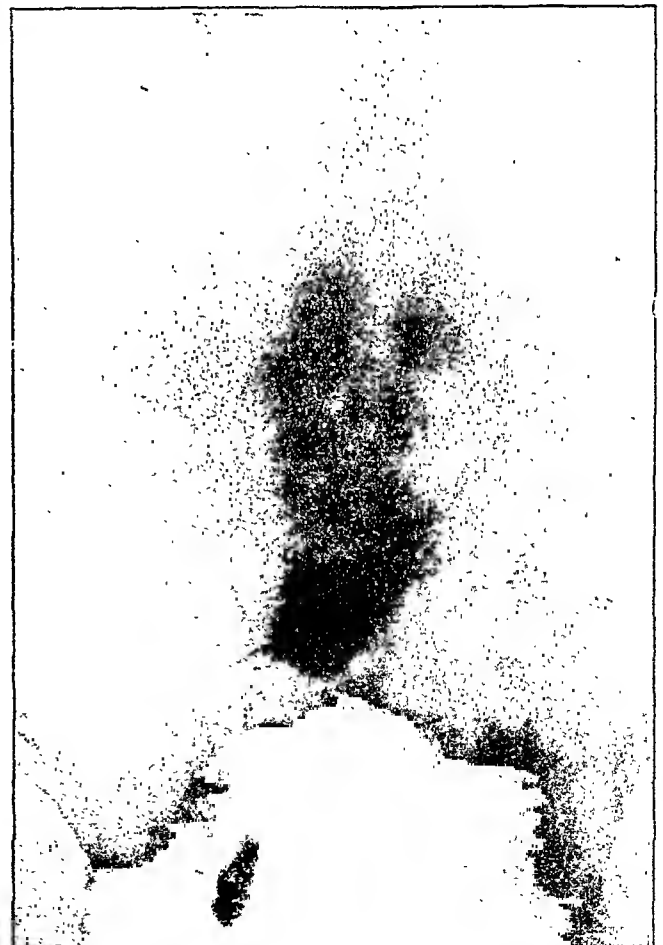


Fig. 2. Three Hour Film.

Fig. 2



Fig. 3

relatively within normal limits. The remainder of the gastro-intestinal series revealed no abnormalities and a detailed description of the other films is unnecessary.

#### DISCUSSION

The roentgenologic signs indicated a partially obstructing lesion at the beginning of the transverse portion of the duodenum. The dilatation of the second portion of the duodenum and the partial dilatation of the cap, and the vigorous gastric peristalsis, all indicated a slowly developing obstruction. This suggested a slowly developing tumor and since the only organ of importance at that exact site is the pancreas, suspicion was directed to a neoplasm in this organ. The next question was the exact location of the tumor. The site of the obstruction indicated very clearly that it was in the mid-portion. The films, as indicated in the figures above, all showed a normal configuration of the descending or second portion of the duodenum, that is, there was not an increased convexity of the second portion producing the capital "C" configuration which is typical of carcinoma of the head.

The next step was the correlation of the clinical data. The absence of jaundice and of a palpable gall bladder militated against the diagnosis of involvement of the head of the pancreas. For these reasons, it was held justifiable to postulate a primary carcinoma, starting in the body of the pancreas and not involving the head.

Fig. 3. Six Hour Film.

The clinical course was rapidly downhill with increasing loss of weight, weakness, inability to eat and diarrhea. There was a temporary improvement following the administration of intravenous glucose solutions but, within a few days thereafter, the patient became moribund and *exitus* occurred without elevation of temperature or pulse rate. Death occurred on December 5, 1934, six weeks after admission.

An autopsy was performed four hours after death (Dr. S. A. Jacobson). Excerpts from the protocol which are pertinent only are given.

**Heart.** The epicardium is everywhere smooth and glistening. A large area over the right ventricle is white and thickened. The small quantity of pericardial fat which is present has been converted into an edematous mass (serous degeneration). Coronary vessels are tortuous and very thick and sclerotic to palpation. On section, myocardium is dark brown and firm. Walls are of normal thickness, but all cavities are diminished in size. The mural endocardium is everywhere transparent. All valves are thin and delicate with the exception of the aortic. One of the commissures of this valve shows a moderate degree of fusion with thickening and hardening of adjacent portions of the cusps. Otherwise, there is no thickening or calcification, even in the mitral ring. All branches of both coronaries show very marked thickening and hardening of their walls, although complete occlusion of the lumen is nowhere demonstrable.

**Lungs.** Both are rather large; except for some consolidated areas in the right, they are crepitant, albeit slightly edematous, to palpation. Apices show some thickening of the pleura. Firm pleural nodules can be felt in the upper portions of the organs, and, in diminishing numbers for a considerable distance downward. On section, the parenchyma is for the most part bright pink and wet. The parenchyma of the apices, however, is dark gray and more or less solid in appearance. Irregular areas of the middle and lower lobes of the right lung reveal upon close inspection areas which are firmer and slightly raised and granular. Bronchial mucosae are smooth; in the lumina is found some thin whitish matter. Pulmonary vessels show nothing noteworthy.

**Liver.** The organ is decidedly reduced in size. On the surface and in the interior are numerous large, sharply demarcated, white tumor nodules which stand out from the cut surface. The parenchyma is dark reddish brown; lobules are clearly demarcated. The gall bladder is considerably distended, as also is the common bile duct. Their walls show no abnormality; they contain thin green bile.



Fig. 4. Photomicrograph of the Primary Carcinoma in the body of the Pancreas removed at autopsy.

Fig. 4

**Suprarenals.** That on the right is normal in size and shape. The cortex is rich in brown matter. That on the left is infiltrated by direct extension with the tumor mass of the adjacent pancreas.

**G. I. Tract.** The esophagus shows nothing noteworthy; stomach contains some greenish fluid; its mucosa is slightly congested; duodenum shows nothing unusual, its mucosa is pale and smooth. The jejunum and ileum are similarly negative, except for the presence of a diverticulum measuring approximately 4 cm. in length, situated approximately 1 meter cephalad of the ileocecal valve. The colon shows nothing noteworthy.

**Pancreas.** The head of the organ is soft, lobules pulling apart readily. The body and tail, however, have been destroyed and replaced by an irregular mass of very hard, white tissue in which yellow areas are visible. This mass does not extend into adjacent structures, with the exception (left suprarenal) noted above.

**Blood Vessels.** The aorta, throughout its length (with the exception of the ascending portion) bears numerous, yellowish and, particularly about the mouths of the intercostal arteries, whitish plaques. A few of these in the lowermost portion are ulcerated. Hardly any of them are brittle. Vena cava and portal vein are smooth; the latter is slightly distended.

**Lymph Nodes.** Those of the hilum of the lungs are large, gray and firm. Those in the vicinity of the pancreas, particularly about (and pressing on) the bile ducts, are infiltrated with white tumor tissue, as are some of the more distant mesenteric nodes.

#### ANATOMICAL DIAGNOSIS

1. Carcinoma of the body and tail of pancreas, with direct extension into left suprarenal gland and metastases to liver and regional lymph nodes.

2. Coronary arteriosclerosis.

3. Brown degeneration of heart and liver.

4. Chronic passive congestion of viscera.

5. Chronic (inactive) pulmonary tuberculosis of both apices.

**Microscopical.** Section of the pancreas (Fig. 4), shows part of it to be in a good state of preservation, except for

a slight degree of fibrosis. There is, however, a large amount of tumor tissue, as indicated in the gross study. This is in part divided from the surviving pancreatic tissue by a thick fibrous septum; in part, however, it has crossed this boundary and infiltrates the parenchyma freely. The tumor consists of glandular elements made up of moderate-sized, somewhat hyperchromatic and pleomorphic, polyhedral cells. Giant cells are very numerous. The architecture is extremely irregular. The amount of fibrous tissue is very variable. Large areas of tumor are completely necrotic.

#### SUMMARY

The outstanding clinical facts were a marked loss of weight, appetite and strength, increasing cachexia and the development of an unexplained persistent and increasing pain located at the level of the lower dorsal vertebrae and radiating up and down the spine for short distances. Later, an identical type of pain, located in the epigastrium, developed which radiated through to the region of the back pain. Both of these pains were aggravated by walking. The roentgen findings demonstrated no osseous change in the dorso-lumbar spine. The gastro-intestinal roentgen examination revealed a partial obstruction at the beginning of the transverse (third) portion of the duodenum with dilatation of the descending portion of the duodenum and of the cap, and increased gastric peristalsis, indicating gradually developing obstruction. Based upon these clinical and roentgen findings, a diagnosis of carcinoma of the body of the pancreas was made. This diagnosis subsequently was verified at autopsy.

#### CONCLUSIONS

1. A case of carcinoma of the body of the pancreas is reported.

2. The diagnosis was made on the basis of the clinical and roentgen findings, and verified at autopsy.

3. It is believed that this is the first case of its kind to be reported.

#### REFERENCES

- Scholz, T.: Zur Röntgenologischen und Klinischen Diagnose des Karzinoms des Schwanzteiles des Pankreas. Bericht eines weiteren Falles. *Röntgenpraxis* (Hft. 24), 4:1043-1046, December, 1932.
- Haring, W.: Die Erkrankungen der Bauchspeicheldrüse in Röntgenbild. *Ergebnisse der Medizinische Strahlenforschung*, 6:407-457.
- Riese, H.: Die Chirurgie des Pankreas. Kirschner-Nordmann, Die Chirurgie (Urban & Schwarzenberg, Berlin), 1927, *idem*.
- Gruber, G. B.: Handbuch d. Spez. Path., Anat. u. Hist. (Henke & Lubarsch), 1929, *idem*.
- Scholz, T., and Pfeiffer, F.: Röntgenologic Diagnosis of Carcinoma of the Tail of the Pancreas. *J. A. M. A.*, 81:275-277, 1923.
- Hebb, R. G.: Cancer of Body and Tail of Pancreas. *Westminster Hosp. Repts.*, London, 16:44-66, 1909.
- Malbot, H.: Contribution à l'étude des cancers douloureux du corps du pancréas. *Bull. et mem. Soc. méd. d. Hop. de Paris*, 27:305-318, 1909.
- Mollard, J., and Rimaud, L.: Cancer du corps du Pancréas. *Lyon Médical*, 64:602-604, 1910.
- Leriche, R.: Etude Clinique sur le cancer du corps du pancréas. *Médecine Moderne*, 21:289-294, 1910.
- Leriche, R.: Studie über das Carcinom des Corpus pancreatis. *Arch. f. Klin. Chir.*, 42:1048-1071, 1910.
- Labbe, M., and Gendron, A.: Cancer du Corps du Pancréas avec Sacrodyne et Crises Apoplectiformes. *Bull. et mem. Soc. méd. de Hop. de Paris*, 34:596-601, 1912.
- Ludin, M.: Die Röntgenuntersuchung bei Pankreaserkrankungen. *Schwed. Med. Wochenschr.*, 64:692-695, 1934.
- Tillier, M.: Du Diagnostic radiologique des tumeurs du Pancréas. *Bull. et Mem. de la Soc. de Radiologie Médicale de France*, 21:623-626, 1933.
- Ernst, G.: Zweckmassige Röntgentechnik zur Diagnose der Pankreatitis und der Pankreastumoren. *Med. Welt.*, 8:794, 1934.

## ABSTRACTS

SAPOZNIK, H. J.; ARENS, R. A.; MEYER, JACOB, AND NECHLES, HEINRICH

*The Effect of Oil of Peppermint on the Emptying Time of the Stomach. J. A. M. A.*, 104:1792, May 18, 1935.

The authors have previously reported that oil of peppermint diminished gastric acidity. In this study they report the effect of oil of peppermint on the emptying time of the stomach. In the empty stomach small doses of oil of peppermint had no effect on the hunger contractions of dog or man. Large quantities of oil of peppermint decreased the motility in six tests and produced no change in two.

In experiments with a meat meal and oil of peppermint, shortening of the emptying time was observed.

In six normal young females the addition of two cc. of oil of peppermint to a barium-milk shortened the emptying time of the stomach as observed fluoroscopically.

These studies seem to explain the popular use of oil of peppermint in many stomach remedies. The use of peppermint candy and peppermint alcohol after a heavy meal appears useful because by increasing motility distension and fullness are relieved more promptly.

Francis D. Murphy, Milwaukee.

# Diverticulum of the Stomach\*

By

ELLIS B. FREILICH, M.D.

GERHARD DANIELIUS, M.D.

GEORGE C. COE, M.D.

CHICAGO, ILLINOIS

**D**IVERTICULA of the stomach relatively are uncommon. They occur in the stomach less frequently than in any other part of the gastro-intestinal tract, with the exception of the jejuno-ileal region.

The first case, pathologically, was reported by Helmont in 1804, Akerlund reported the first case, roentgenologically, in 1923. Since that time, 108 cases have been recorded. In a recent article by Drs. River, Stevens and Kirklin, the subject is statistically reviewed. To the already existing literature they add a series of 33 cases from the Mayo Clinic, of which only 19 were proven as true diverticula.

It is our purpose to report another case accompanied by complete X-ray studies. The diagnosis here was made without surgical aid. We were able, therefore, to go back and re-question the patient in an effort to determine whether or not a typical or a suggestive clinical symptomatology exists to help in future diagnoses. With this in mind, we have also carefully reviewed all the literature with particular study of the case reports. We are mainly concerned with this question for future assistance clinically.

## CASE REPORT

The patient Mrs. M.T., age 29 was first seen by Dr. E. B. Freilich. She complained of cramp-like pains localized to the middle of the abdomen. These pains had recurred at irregular intervals over a period of ten years but always during the fall season. Under codein medication the pains subsided.

On December 15, 1934, the patient was again seen because of severe, excruciating pain in the epigastric region. As much as a half grain of morphine hypodermically was required to control the pain. On the following day the patient was admitted to the medical service of Dr. Freilich at the Mt. Sinai Hospital.

At this time she volunteered the information that she had experienced a similar attack about ten years previously. Since that time, she has had the recurrent attacks of abdominal cramps. The pains were not influenced in any way by food or fluids of any kind, and they were in no way related to the gastric cycle.

Her appetite was excellent and there was no loss in weight. No history of nausea, emesis, hematemesis, jaundice or melena was elicited. The bowel function was fair with a slight tendency toward constipation.

Systemic enquiry was essentially negative. In 1919 she had a tonsilectomy and a submucous resection. As a child she had pleurisy with an endocarditis, but no residual effects were determined.

*Physical examination* revealed a white female, not acutely ill, but markedly nervous and apprehensive. Head, eyes, ears, nose and throat essentially were negative. The heart and lungs were normal in function and action. The abdomen was soft and relaxed with no pain, tenderness or rigidity.

*Laboratory studies* all were negative. Blood pressure was 106/64. Blood chemistry showed 82 mg. sugar and 9

mg. urea nitrogen per 100 cc. blood. Gastric aspiration, after an Ewald test meal, revealed no free hydrochloric acid and but 14 cc. total acidity. Basal metabolic studies were normal with rates of +2 and -3; E. K. G. was normal. The blood count showed 100% hemoglobin, 4,120,000 red cells (I.I.I.), 8,100 white cells with 63% polymorphs, 31% small lymphocytes and 3% eosinophiles. Wasserman and Kahn tests were negative; urine examinations were repeatedly normal.

*Gastro-intestinal X-ray studies* were made and since the diagnosis was roentgenographic rather than clinical, we are quoting Dr. Danielius' report:

"The barium meal passes normally through the esophagus and the cardia. With the very first swallow an unusual globular shadow is visible closely below the entrance of the esophagus into the stomach. It is a perfectly round pocket the size of a hazelnut situated on the lesser curvature, close to the posterior wall of the stomach and is well visualized in all the different positions and directions.

The mucosal pattern of the stomach appears to be completely normal; the rugae soft and sharply limited. Upon complete filling the stomach is seen to be of the fishhook type, the lowermost point being about 1½ inches below the iliac crest. The outlines are sharp in all respects, and the tonus is good. The peristaltic waves run normally along both curvatures as far as the pylorus. The expulsion begins normally. The pylorus, the duodenal cap and the other parts of the duodenum appear completely normal. All parts are freely movable and no pain is elicited upon pressure.

The films very clearly substantiate the fluoroscopic findings. On the film, taken in the recumbent position, small, soft and well defined rugae are visible leading into the diverticulum ("*schleimhautschicne*"). Furthermore the whole mucosal pattern of the stomach is soft, well defined and shows no evidence of irritation.

*On the three hour study* there was an isolated filling of the above described round shadow pocket. Otherwise the stomach had emptied itself completely and the cecum was beginning to fill out.

*On the 24 hour study* the colon was filled from the cecum as far as the descending colon; all parts showed a normal position width, haustrations and sharp outlines.

*The X-ray findings indicate a diverticulum of the stomach* about the size of a hazelnut near the cardia on the lesser curvature close to the posterior wall. No pathologic findings or other diverticula are present elsewhere in the gastro-intestinal tract."

## ROENTGENOGRAPHIC DISCUSSION

In this case we had to decide whether the X-ray findings indicated a penetrating ulcer or a diverticulum. Our reasons for the latter diagnosis follow:

1. The localization closely below the cardia on the lesser curvature more posteriorly is typical for diverticulum. Such anomaly rarely is encountered elsewhere in the stomach. Though an ulcer niche occasionally

\*From the Medical and Roentgenological Services, Mount Sinai Hospital. Submitted March 3, 1935.

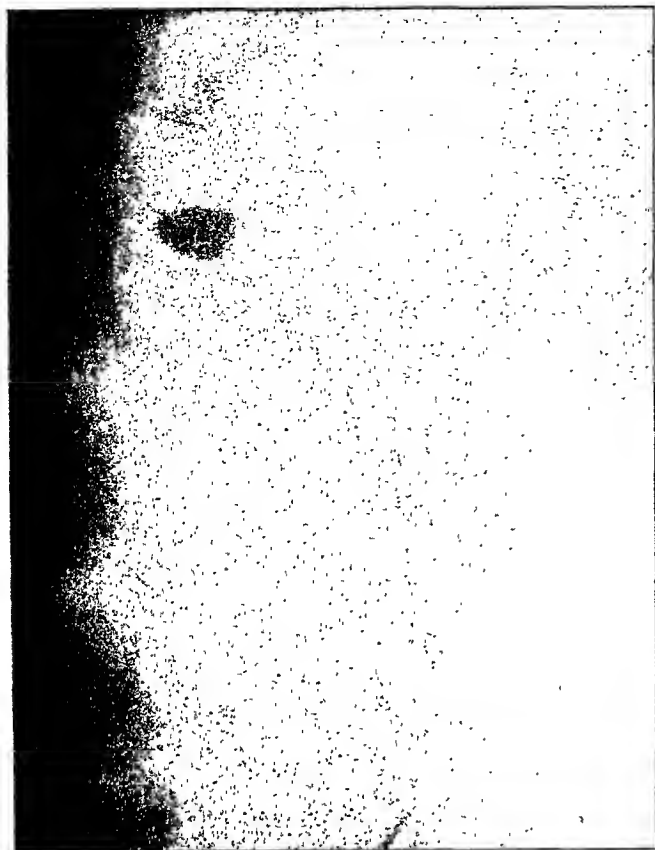


Fig. 1

may be found in this locality, its occurrence is extremely uncommon.

2. The so called "*schleimhautschiene*" (mucosal tract) in the neck of the diverticulum is typical for all diverticula of the gastro-intestinal tract, and corresponds anatomically with a normal, non-involved mucosa. This is not the finding in a penetrating ulcer, where as a rule, the mucosa is destroyed or infiltrated.

3. The regular, perfectly round shape of the shadow suggests a diverticulum, but does not absolutely rule out an ulcer.

4. The complete lack of a gastritis ("*begleitgastritis*") aids in the diagnosis. An ulcer niche of the type of this shadow probably would be combined with findings of a gastritis.

#### CLINICAL DISCUSSION

Diverticula of the stomach may be of congenital (true) or acquired (false) type. The true diverticulum involves all the layers of the stomach and implies intact muscular and mucosal layers. In the acquired type one coat is absent.

Various hypotheses are offered, but the consensus of opinion favors the congenital formation of true diverticula.

The average age group in the series studied at the Mayo Clinic was about 42 (25-59) years. Our patient was 29. Diverticula occur with equal frequency in both sexes. The anatomic location is typically in the cardia just below the esophageal junction on the lesser

curvature near the posterior wall.

Fig. 1. Upper part of the stomach in the upright position. Filling with a small amount of barium. On the lesser curvature near the cardia (on the fluoroscopic view close to the posterior wall) the perfectly round regular pocket is visible, superimposed by a small air-bubble. Mucosal pattern soft, regular and sharply limited.

curvature near the posterior wall.

Carefully reviewing the literature of case reports, we find that there are no typical symptoms clinically pointing towards the underlying pathologic anatomy in the stomach, but there are certain suggestive clues. The patients' complaints cover long periods of time. There are intervals of long duration in which the patients are absolutely symptom free. When the symptoms arise, they come suddenly and equally abruptly disappear. There seems to be a certain periodicity of attacks. The symptoms as a rule are vague (a sense of epigastric discomfort, substernal fullness and stinging, cramp-like distress) and are in no way related to the kind or character of food eaten.

In analysing this question, we find several reasons for the lack of a typical symptomatology.

1. Only in the last few years has it been possible to make the diagnosis of a diverticulum of the stomach without the aid of surgery. In the past most of these were discovered at autopsy, but with the advent of the X-ray, diverticula can be "picked up" early. The number of physicians having had the opportunity to re-question the patient in the light of X-ray diagnosis is still rather small.

2. The types of diverticulum, anatomically, have not yet been subdivided. The symptoms or lack of symptoms will depend upon the width and the length of the neck of the sac, any associated pathology, etc.

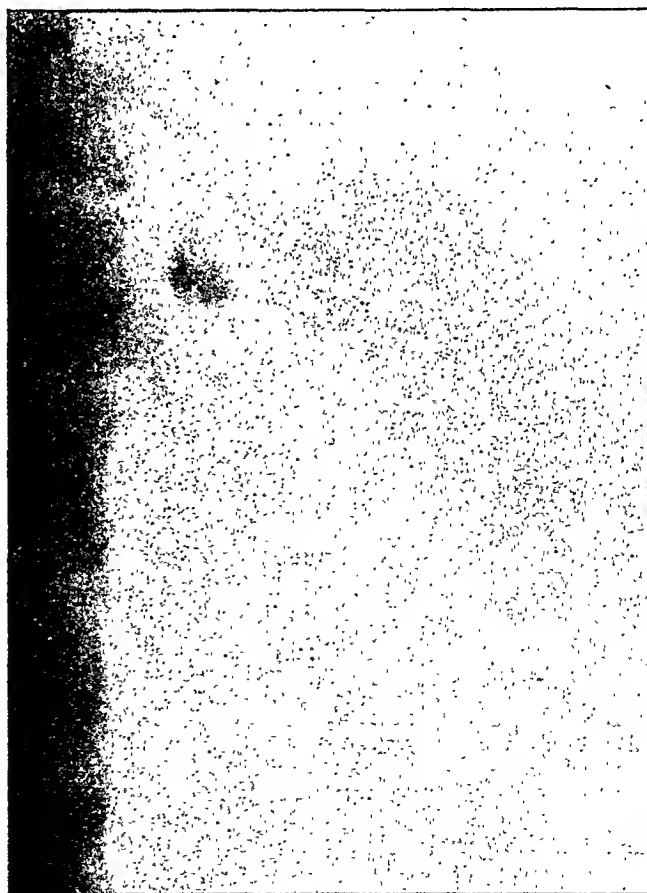


Fig. 2

Fig. 2. Stomach in the recumbent position. The shadow-pocket now crescent-shaped but again perfectly regular. The "*Schleimhautschiene*" (mucosal tract) on the neck of the diverticulum well visualized. The mucosal pattern of the whole stomach soft, regular and presenting no signs of irritation.

A diverticulum having a large neck and no associated irritation of the mucosa, which fills and empties easily, obviously will give rise to few or no symptoms. A diverticulum with a narrow neck, with or without any signs of irritation, may give rise to symptoms. The latter also may be true if there is swelling of the mucosa in the neck delaying or retarding the emptying of the cavity.

3. A true diverticulitis, or even an ulcer in the diverticulum, will give rise to symptoms. Roentgenographically this would be difficult to differentiate from a true ulcer-niche.

## CONCLUSIONS

We are reporting another case of diverticulum of the stomach. The diagnosis here was not made clinically and up to the present time, pre-operatively or ante-mortem can only be made roentgenographically. We feel that by means of the X-ray the diagnosis can be made sufficiently early to give the clinician an opportunity of carefully studying these cases in the hope of building up a symptomatology which will be suggestive, if not diagnostic, of this condition. The matter of differential diagnosis between a diverticulum and an ulcer is important inasmuch as surgical indications are dependent upon the type of pathology present.

## REFERENCES

- Rivers, Stevens, and Kirklin: Diverticula of the Stomach. *S. G. O.*, Jan. 5, 1935. Diverticulum Causing Pseudoulcerous Symptoms. *Bull. A. Mem. Soc. Nat. de Chir.*, 60:580-6, April 28, 1934.
- Gutzeit: Diverticula and Diverticular Formations. *Dtsch. Arch. f. klin. Med.*, 175:291-301, 1933.
- Birnsong: Diverticula, Clinical and X-ray Study. *Wien. klin. Woc.*, 45:1089-91, Sept. 2, 1932.
- Lenarduzzi: Congenital Diverticula of the Stomach. *Arch. di rad.*, 8:444-56, May-June, 1932.
- Laureil: Diverticula of the Stomach. *Act. radiol.*, 12:455-78, 1931.
- Gile: Diverticula of the Stomach. *New Engl. Med. J.*, 204:268-9, Feb. 5, 1931.
- Bruckner: Diverticula Near the Cardia. *Röntg.-Prax.*, 3:13-5, Jan. 15, 1931.
- Benedetti: False Diverticulum (6 cases). *Arch. di radiol.*, 6:523-30, May-June, 1930.
- Bell and Golden: Diverticula of the Stomach. *J. A. M. A.*, 94:534-9, 1930.
- Beutel: Symptomatology and X-ray Diagnosis of Diverticulum Near Cardia. *Fortschr. Röntgenstr.*, 41:630-35, 1930.
- Geyman: Diverticula of the Stomach. *Californ. and West Med.*, 33:813-14, 1930.
- Ottomello: Differential and X-ray Diagnosis. *Poliklinico (Iez. med.)*, 37:482-93, Oct., 1930.
- Stclair: Diverticulum of Stomach in an Infant. *Brit. J. Surg.*, 17:182-4, 1929.
- Liljedahl: Diverticula of Stomach. *Am. J. Roentgen.*, 22:258-9, Sept., 1929.
- Sandstrohm: X-ray Appearances of Diverticula of the Stomach. *Act. radiol.*, 10:427-36, 1929.
- Freedman: Perforating Ulcer Simulating Diverticula. *Amer. J. Roentgen.*, 18:47-51, July, 1927.
- Brandt: Diverticula of the Stomach. *Frankf. Ztschr. f. Pathol.*, 34:527-31, 1926.
- Akerlund: Diverticula of the Stomach From a Roentgenologic Point of View. *Act. radiol.*, 2:476-85, 1923.
- Albrecht: Die Roentgendagnostik des Verdauungskanaals. G. Thieme, Leipzig, 1931.
- Assmann: Klinische Röntgendagnostik der inneren Erkrankungen. F. C. W. Vogel, Leipzig, 1933.
- Berg: (in Mohr-Stühelin: Handbuch der inneren Medizin., Vol. II). J. Springer, Berlin.

# ABSTRACTS

DR. F. GALLART MONES.

*Gall-Bladder Response to Different Stimuli as Detected by Cholecystography, Gaceta Medica Espanola, March, 1935, Vol. IX, No. 6.*

The author concludes after several tests with fats, peptone, plain water, glucose, barium sulphate, dilute hydrochloric acid, hypophysis and adrenalin, that the gall-bladder empties more readily and more quickly with fats than with anything else. He admits that the shadow of the gall bladder becomes smaller after the administration of Magnesium sulphate, through a duodenal tube, but the decrease in size is much more pronounced after fats. Although he believes that patients with gall-bladder disease are benefited by gall-bladder drainage (Meltzer-Lyon), he is of the opinion that the emptying of the gall-bladder alone does not produce this benefit, but that some other factor, perhaps the action of the  $MgSO_4$  on the liver cells, plays an important role.

Juan Rodriguez, Fort Wayne.

RUTLEDGE, C. P.

*"The Diagnosis of Diverticulitis and Diverticulosis of the Colon, with Special Reference to the Roentgen Study of These Conditions." South. Med. Journ., 28:303-309, April, 1935.*

Diverticulosis is defined as the presence of one or more diverticula without symptoms or the presence of inflammatory reaction referable to the diverticula. The presence of diverticula with accompanying symptoms or inflammatory reaction constitutes diverticulitis. The incidence of diverticula has been found to be about one case in every

eighty routine gastro-intestinal examinations. The most frequent location in the colon is in the rectosigmoid region but any portion, even the appendix, may be the site of involvement.

Most cases occur in patients past 40, and usually in men who are overweight and victims of chronic constipation. Diverticulosis generally produces no symptoms. Diverticulitis is evidenced by abdominal discomfort or pain usually about or below the umbilicus particularly to the left and bearing no relation to the intake of food. Constipation is the rule. Bladder irritability frequently accompanies tenderness in the lower abdomen. Muscle rigidity varies. There is often a low grade fever and moderate leucocytosis. Hemorrhage is rare and should suggest the possibility of malignancy. The symptoms may become aggravated or subside.

In the X-ray examination the combined use of the meal and enema give the most information. The enema alone is used in subsiding acute cases or those showing partial obstruction. It is well to remember that there may be several days delay in the filling of the diverticula in rare cases. Areas of spasticity of the colon with numerous serrations (saw tooth deformity) may be the earliest signs of the development of diverticula. In the differential diagnosis the following conditions are discussed—carcinoma of sigmoid, left sided appendicitis, cholecystitis, sigmoiditis, actinomycesis, syphilis, and hyperplastic tuberculosis. A well selected list of references is given.

J. Duffy Hancock, Louisville.



## SECTION V—*Therapeutics*

### Treatment of Hemorrhage Caused by Peptic Ulcer

By

G. A. HENDON, M.D.  
LOUISVILLE, KENTUCKY

NOTHING is more alarming than a copious hemorrhage from an unseen source. No other catastrophe creates such a deep sense of futility in the mind of the physician who is responsible for the patient's welfare.

In hemorrhage from gastric and duodenal ulcers the source of the bleeding in both is invisible and uncertain. Blood simply cascades from the mouth or from the bowel or both simultaneously. The patient becomes cold and blanched and swoons into unconsciousness. The pupils dilate and the respiration becomes slow and shallow and the victim presents almost a perfect picture of dissolution. Blood from the stomach is colored a deep dark red which distinguishes it from that which comes from the lungs. It is often mixed with particles of undigested food. It is a never-ceasing source of wonder that one can lose such apparently large quantities of blood and survive the ordeal. The burden of discretion rests very heavily upon the physician in the case at this particular point and the choice of a proper and safe procedure in the circumstances creates a serious quandary for the medical attendant. The patient presents a very dismal prospect for surgery on account of the acute anaemia and its concomitant infirmities. On the other hand, it seems like unpardonable timidity merely to stand by and watch a patient bleed to death without exerting an effort toward his relief. The medical measures that we have available are so meager that they do not inspire either hope on the part of the patient or confidence on that of the physician.

We have become convinced that there is an efficient solution of the problem furnished by venoclysis when it is used sincerely and appropriately. Complete rest for the stomach is, thereby, secured and the organ contracts into a hard mass which plugs the vessels and controls the bleeding, if allowed to remain in force as much as ten days. All evidences of gastric disease disappear if the ulcer is not malignant. In support of this statement I beg to submit the following twelve cases of hemorrhage which have occurred as the leading symptoms in my series of forty-six cases of gastric and duodenal ulcer treated by venoclysis.

*Case I.* was a physician, age 53, of the stout and robust type. Had had his gall bladder removed and a gastroenterostomy to control hemorrhage three years previously by another surgeon. In the interval he had suffered consider-

able digestive trouble. Was restricted to a diet. Suddenly on Oct. 26, 1932, he collapsed from the effects of a copious hemorrhage. He lost consciousness, became pale and apparently lifeless. His body surface was cold and clammy. He vomited blood and passed large quantities per rectum. His pulse was soft and feeble and he had sighing respiration and gasped for breath. The question of moving him to a hospital was seriously debated on account of the apparent hopelessness of his condition. He was removed however and on his arrival there his blood count showed the red under two million and the hemoglobin 60%. He was immediately started on venoclysis, 10% Glucose in Ringer's Solution and 10 cc. of 10% calcium gluconate was added to each 800 cc. of the Solution.

A diagnosis of marginal ulcer had already been established by X-ray examination. In January, 1934, he had a slight hemorrhage from the bowel. With that exception he has been perfectly well to date, has been symptom-free and weighs 175 pounds: a gain of 45 pounds since his illness and is actively engaged in the practice of medicine.

*Case II.* H. G. E., age 52. After an indefinite period of gastric symptoms he suddenly became dizzy and nauseated and vomited blood copiously, also passed large quantities from the bowel. This began on Feb. 15, and continued through February 16 to extreme weakness and unconsciousness. On February 17, he was removed to the Deaconess Hospital and treated by Dr. R. L. McCormack who exhibited venoclysis. Continued it ten days. Hemorrhage was immediately controlled. All symptoms finally subsided and March 17 he was up and around and on April 15 he weighed 165 pounds. He since resumed his work, has been entirely free from gastric symptoms. It is now three years since his illness.

*Case III.* W. H. W., age 31. Admitted to St. Anthony's Hospital December 18, 1932. Symptoms began four years previously and continued with more or less severity. Two and one-half years ago patient suffered a rather severe hemorrhage followed in a few days by a second. He was temporarily relieved by a Sippy diet treatment. Venoclysis was begun on December 18, 1932, following his third and last hemorrhage. It was continued ten days. He left the Hospital January 14, 1933. He has regained his normal weight and resumed his occupation. Has remained symptom free up to now.

*Case IV.* W. E., age 59. Admitted November 17, 1931. Had peptic ulcer and hemorrhage ten years ago. Has had stomach trouble in varying degrees of severity since then. Present attack began on November 17, 1931. Was brought to hospital in collapse and unconscious. Pulse could hardly be felt at the wrist. Patient was cold and very pale. Venoclysis was immediately begun. There was a prompt reaction on the part of the patient. His progress toward recovery was unbroken. He left the hospital in two weeks.

Venoclysis continued five days. He has gained forty pounds and has remained well up to this time.

*Case V.* A. Z., age 41. Admitted March 29, 1931. Patient has been complaining of "stomach trouble" the past ten years. Has had copious hemorrhages at irregular intervals during the past four years. More frequent and copious during the past year. When admitted to the hospital his R.B.C. was 900,000. Hemoglobin 18%. Venoclysis was begun immediately after his admission. On April 2, a blood transfusion with citrated blood was given through the venoclysis attachment. 500 cc. taking about four hours to give it. He immediately became very restless and became delirious and died on April 4. He had been quiet and composed until the blood transfusion was administered. No post mortem was obtained.

*Case VI.* H. H. A., age 59. Admitted February 22, 1930. Died two hours after admission. Gastric hemorrhage. Diagnosis Peptic ulcer. This patient had a perforation of his ulcer three weeks previous. Was treated by venoclysis and apparently recovered. At that time he had considerable peritonitis was very low in vitality and a surgical operation did not seem advisable. He apparently recovered and was home about one week when he was suddenly seized in the night with abdominal pain and passed large quantities of blood from the bowels. He was taken to the hospital immediately but his condition was so grave on arrival that active measures did not seem justified. Venoclysis therefore was not begun. This case is included because three weeks previous venoclysis had been employed. No post mortem was obtained.

*Case VII.* Jesse B., age 25. Admitted June 11, 1929. Sent to hospital on account of gastric hemorrhage. Seven hours after admission he had a copious hemorrhage from the bowels and for a time pulse could not be felt at the wrist. Venolysis was started immediately and continued until June 19. Had return of epigastric pain June 20 and 21. Venoclysis again exhibited and continued until June 25. Patient left the hospital June 27 and has remained well and symptom free to this date.

*Case VIII.* Geo. S., age 27. Admitted September 21, 1931. Severe gastric hemorrhage. Diagnosis peptic ulcer. Since May, 1931, patient has had numerous hemorrhages accompanied by much nausea and vomiting. Has had retinal hemorrhage in both eyes. Venoclysis used seven days. November 17, 1931, patient was dismissed from the hospital. Patient has remained well since that time and now seems normal in every way.

*Case IX.* Leo M., age 30. Admitted June 2, 1934. Very severe gastric hemorrhage two days before admission. Diagnosis: Peptic ulcer. Pain in epigastrium for the past year. Pain and nausea appear soon after he takes food although appetite has been good. Highly seasoned food causes the most pain. Has noticed tarry stools on numerous occasions during the past three months. Symptoms have increased recently both in frequency and severity. He was discharged from the U. S. Navy on account of T. B. pleuresy. He uses alcoholic drinks to excess. This is the only case in this series in which the X-ray failed to show evidence of lesion. The clinical symptoms were so positive that I can not escape the conclusion that he had an ulcer. Venoclysis was begun June 3, 1934, and discontinued June 11, 1934. He left the hospital June 16, 1934. Although he has resumed his drinking habits, he remains free of symptoms and has gained thirty pounds. I predict from him an early relapse of symptoms.

*Case X.* P. K., age 48. Admitted February 28, 1929. Diagnosis: Peptic ulcer. Has had gastric symptoms seven years. Has epigastric pain which occurs one to one and one-half hours after meals. Ingestion of food or soda gives relief temporarily. Pain occurs frequently at night about an hour after going to bed. Has had five copious hemorrhages from the bowels in the past four years. The last one occurred one year ago and was the most severe of all. Drinks alcoholics to excess. Gets on protracted sprees, when he can obtain the money. He had venoclysis from

March 1, 1929, to March 7, inclusive. He left the hospital March 15. His symptoms were relieved. However, he resumed his drinking habits and died two years later of delirium tremens and pneumonia combined, having had several intestinal hemorrhages in the meantime.

*Case XI.* F. S., Louellen, Ky., age 43. Mine Supt. Treated at Harlan Hospital July, 1934. Referred by Dr. W. M. Martin. Without warning this patient was taken suddenly ill with violent hematemesis. I saw him about twelve hours later, he was then unconscious, very pale and pulse could scarcely be distinguished at the wrist. Venoclysis was immediately begun and I returned to Louisville after giving explicit instructions in regard to the management of the case and the conduct of venoclysis. The patient made steady progress toward recovery and later regained his weight and resumed his occupation and has remained well since then.

*Case XII.* Mrs. M. L., age 66. Admitted January 4, 1930. Nurse by profession. Severe hematemesis. Peptic ulcer diagnosed. Vomited a large quantity of blood, some of it clotted. Venoclysis immediately exhibited and continued five days. Hemorrhage promptly controlled and general improvement was established and she left the hospital January 20. Resumed her occupation as professional nurse. She appeared to have made a complete recovery. February 17, 1935, five years after her treatment, she called me to her, where I found her prostrated from a severe gastric hemorrhage. She was immediately removed to the hospital and venoclysis begun. She had some bleeding the first day. Then all bleeding stopped. Her temperature assumed high peaks, 104-105-106; venoclysis was discontinued on the third day. The patient died five days after admission. Post mortem disclosed an ulcerating cancer and her intestinal tract filled with clotted blood.

## COMMENT

In all cases 10% Glucose in Ringer's Solution or normal Salina was the solution employed. Dilaudid in small doses was used as needed for its quieting effect.

The four deaths occurring in this series might be analyzed as follows: Case XII, was 66 at the time of the first treatment, was free from symptoms five years and died at 71, from cancer of the pylorus and hemorrhage.

Case X, lived three years and died of alcoholic excess and pneumonia.

Case V, was bled down to 18% hemoglobin and less than a million red cells when admitted.

Case VI, was beyond human aid when seen and did not have venoclysis.

The other eight cases so far as I can determine are restored to their normal state of existence.

Although I have done so previously, it might be appropriate at this junction to offer an explanation in regard to venoclysis. I quote the following from my paper read at the annual session of The American Medical Association, June 25, 1930:

"Venoclysis is a term which I have employed to designate for the biologic and continuous administration of physiologic and therapeutic solutions directly into the blood stream." My experience with this "means of graec" covers almost the entire range of surgery. We have been able to support life and maintain a fair degree of physical prosperity for as much as three weeks at a time, to the exclusion of all other sources of nutrition. We have used it for the treatment of forty-six cases of gastric and duodenal ulcer which includes the twelve cases herein reported. In this series we had only one death besides those reported in this paper and that particular patient proved to be a cancer instead of an ulcer.

In all my cases X-ray studies have been made to verify the diagnoses.

I am convinced that venoclysis as a routine treatment for bleeding gastric and peptic ulcer is preferable to any yet presented. The risk is less, the time is shorter and the cures forty-one out of forty-six treated is better than any other statistics yet reported. I am greatly strengthened in my belief when I consider that my histories extend back six years.

The subsequent treatment after venoclysis has been discontinued, consists in certain gradations of restricted diet, beginning with liquid the first day then soft diet, light and given at regular intervals. The patient is instructed after returning home to avoid coarse articles of food or substances that may traumatize the mucous membranes. Perhaps celery might be classed as an example of what I mean. All fibrous or harsh substances are prohibited. We find the patients

are very happy if allowed such things as rice, mashed potatoes, toasted bread, puddings, eggs, chopped meat, fish or chicken, etc. I had one patient who gained a pound a day after returning home on squirrels and mashed potatoes and he shot the squirrels himself.

My experience in checking the chemical reaction of the gastric secretions leads me to the conclusion that the administrations of alkalies to secure and maintain alkalinity is not justified by the evidence. The clinical progress of my patients has not been influenced either way by their gastric juice reactions. Some of my cases have become alkaline in their gastric chemistry and remain so throughout, some have retained their acidity, some have changed from alkali to acid and no difference could be observed in the progress toward recovery. All our cases of marginal ulcer were alkaline in the beginning and later became acid but had relief of symptoms.

## ABSTRACTS

### SYMPOSIUM ON LEAD METABOLISM AND LEAD POISONING

1. A. J. Lanza, M.D.—Epidemiology of Lead Poisoning. *J. A. M. A.*, Vol. 104, No. 2, p. 85.
2. Joseph C. Aub, M.D.—The Biochemical Behavior of Lead in the Body. *J. A. M. A.*, Vol. 104, No. 2, p. 85.
3. Frederick Thamann, Ch. E. and Jacob Cholak, Ch. E.—Normal Absorption and Excretion of Lead. *J. A. M. A.*, Vol. 104, No. 2, p. 90.
4. Roy R. Jones, M.D.—Symptoms in Early Stages of Industrial Plumbism. *J. A. M. A.*, Vol. 104, No. 3, p. 195.
5. Irving Gray, M.D.—Progress in Treatment of Plumbism. *J. A. M. A.*, Vol. 104, No. 3, p. 200.
6. Elston L. Belknap, M.D.—Control of Lead Poisoning in the Worker. *J. A. M. A.*, Vol. 104, No. 3, p. 205.

The newer knowledge in this field relates to the metabolism of lead especially in regard to its deposition in bone and its excretion in feces and urine, the methods of artificial deleading and the modern prophylaxis in industry by periodic examinations of blood and urine. The essential points may be summarized as follows: 1. Lead is ingested in food in a daily amount of .176 mg. to .25 mg. About the same amount is excreted daily in the feces and a daily amount of .05 mg. to .1 mg. (observations on medical students) is excreted daily in the urine. Hence normally a lead equilibrium is established. 2. With excessive lead intake there is retention, e.g., 473 mg. ingested gave an excretion of 69 mg. in 46 days. 3. Lead is found as a soluble diphosphate in the blood and like calcium is deposited within a few days in the bones as an insoluble tertiary phosphate. 4. Mercury and radium like lead and calcium are absorbed by and deposited in bone. The metallic salts are deposited in the trabeculae in marrow especially of the epiphyses. 5. Lead and calcium are stored or withdrawn from the bone simultaneously and under similar conditions. 6. Lead stored in bone is not toxic except possibly as a cause of dental caries. 7. Excretion is mainly through the feces, less in the urine. The quantitative estimation of lead however is more practical in the urine. 8. Lead excretion may be hastened by acid producing agents especially ammonium chloride and phosphoric acid. High calcium intake in diet or by intravenous injection reduces lead excretion and controls toxic episodes. 9. Calcium gluconate, intravenously 210 cc. of 10% may give a very dramatic relief in acute lead colic

or other symptoms. Fifty cubic centimeters of 5% calcium gluconate intravenously every four hours for two days have been used, then less frequently and finally by mouth. 10. Parathyroid extract and viosterol increase the excretion of lead, mercury and radium. 11. Metabolic crises and acute infections release lead from bone trabeculae. 12. Lead can be "pulled" from bone two years after known exposure has been stopped. 13. Artificial deleading should be done one to four weeks after the subsidence of acute symptoms by low calcium diet and by the administration of ammonium chloride or phosphoric acid, aided if necessary, by parathyroid and viosterol. Ten cubic centimeters of ten percent phosphoric acid may be given in diluted form every hour for ten doses and magnesium sulphate one-half ounce every morning. 14. Deleading should not be done continuously for more than four days at a time and only once a month. 15. Six to fifteen courses of deleading may be necessary. It may never be complete but symptoms are permanently controlled and the period of disability reduced by half. 16. Symptom free "insusceptibles" may have large quantities of lead stored in bone ready to be liberated by artificial or spontaneous deleading. Clinical symptoms are essential in diagnosis. Toxic symptoms do not necessarily parallel absorption and excretion rates. 17. The toxic dose of lead is only one to two mg. daily if continuous over a period of several years. 18. Lead is absorbed mainly by inhalation, less by ingestion, very little by absorption through the skin, except in special form such as tetra-ethyl-lead. 19. Prophylactically in lead industries air analysis for lead dust may be made and respirators used when necessary. Reticulocytosis is one of the earliest signs. Stippled cells are regarded as one form of reticulocytes. An intravenous lead injection may cause as high as 30% reticulocytosis and a transient polycythemia. 20. Lead in the urine in excess of .2 mg. in a 24 hour specimen is a danger signal. The modern industrial physician aims to keep it well under .1 mg. per day. 21. Interval examinations of blood and urine in lead workers are of great value in controlling clinical lead poisoning and illustrate the principle of periodic health examination in industry.

V. C. Rowland, Cleveland.

## SECTION VI—*Abdominal Surgery*

### Factors Pertinent to the Reduction of the Mortality in Cholecystectomy\*

By

MOSES BEHREND, M.D., F.A.C.S.  
PHILADELPHIA, PENNSYLVANIA

THE chief factor, concerning the reduction of the morbidity and mortality following the operation of cholecystectomy is the acquisition of an intimate knowledge of the anatomy of the bile passageways. The best way to obtain this knowledge is the study of anatomical specimens gained from dissections and animal experimentation. Nothing can supersede the intimate knowledge derived from personal dissections in the anatomical laboratory.

While teaching anatomy in the Baugh Institute of the Jefferson Medical College, it was my privilege to observe the anatomical relations of the bile ducts and blood vessels in about 400 cadavers. In these, it was demonstrated that while normal relations were observed in 75% of bodies examined, there were 25% of anomalies; these anomalies undoubtedly account for many mistaken identifications occurring during operation. However, these alone are not responsible for the sole errors in technic, because even where we have normal relationships of the bile passageways, our errors are frequently those of commission, as well as of omission.

Is there a way to avoid these errors in technic? If we never fail to incise the right free border of the gastro-hepatic omentum, the cystic and common ducts are uncovered, which immediately allows us to see the relationship of the cystic duct to the ampulla of the gall bladder. The gall bladder should never be removed unless this relationship of the cystic duct entering the ampulla of the gall bladder is observed. The cystic duct should never be clamped within its peritoneal coat, but instead the "open" operation should be performed. I still observe too many surgeons performing the operation of cholecystectomy within the folds of peritoneum hiding the cystic and common ducts. By means of the "open" operation the common duct ought never be in danger of being incised, ligated or destroyed. And this applies as well in those cases where the peritoneum, covering the ducts, as a result of inflammation is much thickened and indurated, thus resulting in a sort of homogeneous mass at the site of operation. In these cases it is also important to incise the thickened peritoneum with a knife and then, by blunt dissection with a long curved scissors, the

cystic and common ducts reveal themselves to the full view of the surgeon.

#### SPINAL ANESTHESIA

There is no question in my mind about the efficacy of spinal anesthesia to reduce the mortality and morbidity in operations on bile passage-ways. The ease with which operations can be performed under "spinal" undoubtedly saves lives. For one thing the liver is not traumatized; this I believe has been one of the causes of so-called "liver deaths." Great care, however, must be exercised, that on account of the resultant relaxation, the common duct be not mistaken for the cystic duct and thereby destroyed or injured. Precaution as outlined in the previous paragraph will obviate the great majority of accidents.

#### GLUCOSE

The administration of glucose by veneclisis and hypodermoclysis before operation has the beneficial effect of making the liver more tolerant to traumatism. The maintenance of the glycogen reserve is important in all operations on liver and bile passageways. Glucose is given usually on three successive days before operation in doses of 500 cc. of 5% strength when given under the skin and by proctoclysis and 10% when given into the vein. An important article has just been published by Cutting on this subject. He states that a 5% solution is isotonic and is readily absorbed by the bowel. It was always my impression that dextrose was absorbed through the intestinal tract. This was proven to my satisfaction in a case where a cholecystostomy had been performed. While proctoclysis was being given, large quantities of the fluid were excreted through the fistulous opening. The objection to proctoclysis as I see it, is the lack of co-operation one gets on the part of the patient in retaining the fluid. It seems, however, in some cases no matter what procedure is employed, patients cannot retain the fluid given by proctoclysis, so that this method practically has been abandoned now for the introduction of fluids by veneclisis and hypodermoclysis.

#### ACUTE CHOLELITHIASIS, ACUTE CHOLECYSTITIS, ACUTE EMPYEMA

At present a wave of enthusiasm is permeating the profession concerning the emergency treatment by operation of these acute cases. I want to sound a note of warning against such a procedure. For many years I have maintained that acute cases should not be oper-

\*Read before the Post-Graduate Medical Assembly, Geisinger Memorial Hospital, November 1, 1934.  
Submitted March 25, 1935.

ated on immediately because the dangers of operation are greater than when symptoms have been allowed to subside. Fine dissections cannot be made on hard, turgid gall bladders and their surroundings; isolation of the ducts becomes practically impossible; the danger of spilling pus is always imminent; rapid lymphatic, generalized infection results if the gall bladder is removed. If not removed then an incomplete operation is the result. Only a few days ago, a patient who had been operated on in another hospital for acute empyema presented herself. She stated that she was "terribly sick" following the operation and was not expected to live. Her gall bladder had been drained. I removed the gall bladder which was filled with stones the size of walnuts. By allowing the inflammation to subside however, operations on acutely ill patients can always be completed; on the other hand, with the conditions reversed, it becomes necessary frequently to perform the unanatomical operation, namely that of removing the gall bladder from above downward. Such a procedure may lead to considerable oozing which masks the field of operation and thus may lead to unforeseen technical errors.

### PERFORATION

Perforation about which we read so much at present can be avoided, or at least greatly lessened, in acute cases, if we take away absolutely all food and liquids. I have never failed to see a subsidence of acute symptoms, if the patient were hospitalized. To illustrate. A patient was seen by me in consultation last week. He had been given liquids by mouth; in the presence of intense pain in the right hypochondriac region. His temperature was 102° F. A huge gall bladder easily could be outlined. He was admitted to the Jewish Hospital in the evening when the strict regime just mentioned was begun. The following morning with veneclysis, hypodermoclysis and absolute abstinence of food or drink by mouth, the temperature had dropped almost to normal, the pulse followed; tenderness and rigidity had markedly subsided. Within a few days the patient will be ready for operation. With due respect to the internist, I believe the only way to treat these acute cases is to put them under the absolute care of the surgeon and hospitalize them. Daily consultation with the internist for these seriously sick patients is encouraged.

### THE COMMON DUCT

The advice given by Lahey that practically all common ducts should be opened and examined for stones will lead to increased mortality. The "occasional" surgeon is not sufficiently experienced in operating on common ducts. No surgery is more difficult than this type of work. Much can be learned from the history. If in addition it reveals the presence of jaundice at any time, the common duct should be explored. Much information can be obtained from palpation of the common duct.

### DRAINAGE

Drainage after operation on the gall bladder is rarely used now; exceptions are those cases where there is considerable oozing, or when there has been leakage from the ducts. The omission of drainage after operations reduces mortality because the occurrence of subhepatic and subphrenic collections has been

eliminated. Never have we been compelled to open a case where no drainage was employed. On the other hand, on several occasions when drainage was used, after the drain was removed and the wound had healed, operations had to be performed for secondary collections.

### JAUNDICE

The mortality can be greatly reduced if we do not perform cholecystectomy in the presence of jaundice. Jaundice complicates the operation because of the uncontrollable oozing that occurs in a certain number of cases. For the control of such bleeding nothing is better than blood transfusions. For several years I have discontinued the use of calcium before and after operation in jaundiced patients.

### REPORT OF DEATHS

Since my last published paper (1) on this subject I have had two deaths, the first in 34 months. One case, a woman, was admitted to the Jewish Hospital on the Medical Service for acute empyema of the gall bladder. She had a shattered heart with the presence of fibrillation. Repeated consultations were held between the internist and the surgeon. She remained on Medical Service for three weeks before being operated on. She was thoroughly prepared by means of glucose; cardiac support was given before and after operation. She died one week after operation.

The other case was also that of a woman about 45 years of age, admitted to the Mt. Sinai Hospital, with severe upper abdominal pain. On physical examination the entire right side was rigid and tender. Blood urea nitrogen was 84, which dropped to 15 in about 10 days. She was then operated upon. While the blood urea nitrogen was high she was confused, depressed and could not answer questions intelligently. The gall bladder, filled with stones, was removed. She died of a massive atelectasis.

These patients did not die as a result of technical errors, but rather from an unforeseen complication in the last case and from a not unexpected complication in the first case, because of the fibrillation before operation. The low mortality does not mean an evasion of cases that were poor risks. This applies to those cases also that were admitted to the Philadelphia General Hospital; the physical conditions of these patients is not the most desirable for serious operations. Cases of carcinoma of the bile passageways are not considered in the estimation of mortality.

The mortality also can be reduced by removing the gall bladder within its peritoneal fold. In this manner the bed of the gall bladder is not lacerated. It has been shown that deaths have occurred from the rapid absorption of inflammatory products through the lymph channels. Most of us are familiar with Dr. Max Thorek's technic. He leaves the posterior wall of the gall bladder attached to the liver and fulgurates it before suturing the edges of the liver. He believes that in this way he avoids death because of the sealing of the lymphatics. In a paper read before the American Congress of Physical Therapy held in Philadelphia recently, he reported 90 cases so operated upon without a death.

### CONCLUSIONS

There are certain axioms in gall bladder surgery which if adhered to, will in my opinion, reduce the mortality.

These are:

1. An intimate knowledge of the common and special anatomy of the bile passage-ways.
2. Spinal anesthesia because of the relaxation it affords, has greatly reduced the mortality.
3. Glucose and blood transfusions before and after operations are of great value.
4. Do not operate as an emergency on acute cases.
5. Put the stomach and intestinal tract at absolute rest.

6. Do not explore the common duct unless there is some very good reason.
7. The less we institute drainage, at operation, the better.
8. Never perform a cholecystectomy in the presence of jaundice.
9. Whenever possible remove the gall bladder with in its peritoneal fold.

#### REFERENCE

1. Behrend, Moses: "Acute Inflammation of the Gall Bladder. Conservative Operative Treatment." *Ann. Surg.*, 99:925-929, June, 1934.

## ABSTRACTS

BOLAND, FRANK K.

"The Interpretation of Abdominal Pain." *South Med. Journ.*, 28:133-138, Feb., 1935.

Pain is generally the chief guide to the surgeon that he is dealing with a surgical condition in the abdomen. Errors in diagnosis result principally from lack of knowledge and lack of care, especially the latter. Symptoms referred to the digestive tract are attributed to (1) close anatomical relationship with contiguous structures for example, kidney, ureter, or diaphragmatic pleura; (2) influences traveling through the blood stream, as certain allergic conditions, acute diseases as measles, lead poisoning, undulant and rheumatic fevers, malaria, and arachnidism; and (3) factors dependent upon the nervous system—the digestive tract being unique in that it has both sympathetic and parasympathetic fibers. Conditions to be considered under the general heading of this last group include pneumonia, psychoses, the gastric crises of tabes, herpes zoster, cord tumors, vertebral disease, and sequelae of phrenic nerve operations. Head's law of referred pain is quoted and explained. In discussing the differentiation between cardiac and gall-bladder disease he quotes Vest's statement that "the rank and file of the profession realize neither the significance of the relationship nor the necessity for thorough study and evaluation of both organs when either presents symptoms".

The article is closed by the summarization of several cases illustrating some of the conditions mentioned previously in the paper.

J. Duffy Hancock, Louisville.

D'ABREU, A. L.

*Surgical Aspects of the Spastic Colon and the Prediverticular State.* *Lancet*, 227, Dec. 22, 1934 1385-88.

This paper deals with that group of patients sometimes suffering from leftsided abdominal pain, blood and mucus in the stool and diarrhoea. They are frequently diagnosed vaguely as "colitis".

The commonest patient of this type is the fat middle-aged muscular man, athletic in his younger days. X-ray is indecisive, arcas suggestive of the prediverticular state which Spriggs and Marxer have described as "a ragged outline of the bowel which does not dilate even in the most favorable position" and in which normal segmentation is lost, may be seen.

Laparotomy when performed under spinal anaesthetic reveals a definite pathology. Reddened areas of the colon are seen which from time to time pass into severe spasm. Such pathology is not seen if general anaesthesia

is used for then the parasympathetic impulses necessary for this peristaltic action are lost. In portions of the bowel in the prediverticular state removed along with areas of established diverticulation the most notable change seen is hypertrophy of the circular muscle coat which projects as bands into the lumen of the bowel.

What causes this hypertrophy? There is some evidence to support the theory of parasympathetic overaction. Deficiency of the parasympathetic nerves has been shown in cases of megacolon. Megacolon has been experimentally produced by cutting the parasympathetic nerves to the colon in cats. Vagatonics show hyperchlorhydria, pylorospasm and spastic colon.

In conclusion, it is seen that, in many cases of colon dysfunction, spasm and overactivity of the circular muscle of the bowel play an important part and are factors of the greatest importance in the development of diverticula. The cause of this may be parasympathetic overactivity.

John J. Day, Montreal.

EBELING, W. W., M.D.

*Absorption of Dextrose from the Colon.* *Arch. Surg.*, Vol. 29, No. 6, Dec., 1934, pp. 1039-1047.

This article is a report of a series of experiments done on a chronic colon loop to determine the absorption of dextrose from the colon.

From these experiments, it was shown that the ratio of absorption of dextrose from the colon increased slightly with increasing concentrations up to 5 per cent, which approximates an isotonic solution. With increasing concentrations beyond this point, there was a decided increase in the rate of dextrose absorbed. It was further shown that with an increase in the volume of the solution, concentration remaining constant, there was a decided increase in the amount of dextrose absorbed.

A comparison of the results found in this group of experiments as compared with a previous group, showed that anesthesia per se made little difference in the conduct of the colon as a physiologic unit.

It was also shown by comparing these results with a previous series done by Ravdin on absorption from the ileum or jejunum.

The author feels that as the result of his experiments, the colon as a means of introduction of dextrose into the body mechanism is inadequate for clinical needs and further actual harm may result in the use of hypertonic solutions owing to the large withdrawal of water.

N. W. Swinton, Boston.



## SECTION VIII—*Editorial*

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastroenterological Association is in no way responsible for editorial expressions.

### ADVERTISEMENTS SHOULD BE READ

THE opening of an elaborate and important new research laboratory by one of the world's leading manufacturers of biologicals and pharmaceuticals, re-emphasizes the degree to which the modern producer of therapeutic agents has become the "post-graduate" or the "continuation" avenue through which investigations initiated in educational institutions are carried to practicality, and thence to physicians.

Sera, bacterins, glandular derivatives, germacids, cardiovascular-renal medicines, vitamin-rich substances, foods devised for special purposes, roentgenological and actinological apparatus—and a host of other aids to the diagnosis, prevention and treatment of disease—all are made available in our professional practice because forward-looking, approachable and soundly established concerns are alert to recognize new trends, to new methods, to welcome original, promising ideas. Even though physicians not rarely find it difficult to keep abreast of unique therapeutic principles and preparations and even though, at times, they believe that products are distributed before their specific worth altogether has been proved, yet none denies that our profession would be in a sad way, from the diagnostic and treatment angles, were not a conscientious, hard-working group composed of both scientists and business men constantly striving to progress and to improve.

So generally distributed are our industrial chemists (pharmaceutical manufacturers) and our industrial mechanics (apparatus makers) and so dependable are their products, that, perhaps, we are too apt to take them for granted, failing to realize not alone the tremendous capital needed to keep going these enterprises but also the very essential service which they contribute to the physician's management of the ill or to humanity in general.

It would seem but proper that occasionally, when we open a package of a medicinal or biological preparation which, with all confidence, we may employ and by whose exhibition we improve our standing as physicians, we give thought to what steps already have been taken, and *by how many people*, before that particular agent reaches our hands. Those steps constitute a modern romance: the collection of the potent substance "in the raw," the discovery of its usefulness, the multitudinous processes necessary to prove actual values, the contact with those who are willing to risk capital on advanced research or mass production (for often indeed consideration of substances or ideas proposed during a decade will show that great sums are expended upon what eventually proves unworthy or impracticable), the intricacies of manufacture, the handling and packaging, the distribution and sale. It is a long, long trail which has been trodden before the physician has before him in a syringe, a powder, liquid or tablet the therapeutic agent whose

possibilities were appreciated by some keen mind, whose "mother substance" was snatched from the humid, fever-ridden marshes bordering the oozy African Congo or sliced from a yet quivering carcass amid the sickening scenes and confusion of a huge abattoir.

The patient "detail man" may bring before the doctor what is "new" in therapy but commonly, notice of these modern miracles reach him *via* the advertising pages of the medical journals.

*And he should read these advertisements!* For today, they are not constituted of the medicine wagon lingo of our early memories. Through them, firms tell truths, simply, efficiently and tersely—not alone because actually they wish to inform physicians but because no professional critic of their announcements is so scrutinizingly relentless as are those of their own craft. By whatever criteria their products may be classed by "boards" or "councils," no check upon loose or careless claims, boasts and exaggerations or composition or methods of manufacture approaches in severity that of concerns engaged in like enterprises. It is their *competitors*, not medical organizations or individual doctors, who classify firms and their ads as "right" or "off color."

*Medical publications depend largely for their existences upon advertising revenue.* This Journal has sought to protect its advertisers, by seeing to it that they are kept in "right" company. By so doing, also, it has protected its readers from the intrusion upon their time and ethics, and from insulting their scientific training and experience: complications sure to follow by the admission to its advertising pages of the swarm of "twilight zone" firms which swoops down upon every legitimate medical publication. If such firms can get into the company of "right" advertisers, they conclude that physicians will accept the stuff which they announce as "right." This policy of "selective exclusion" has proved very costly to this magazine's publishers, but they are convinced that it is appreciated, both by our advertisers and our readers. The policy will be maintained. The advertising pages must be kept in tune with the high order of the Journal's scientific text.

Finally, there is no question that readers owe great debts of gratitude to firms and institutions who maintain the highest possible standards of scientific manufacturing and ethics and whose ideals rise above mere dollar-making. Particularly should our readers be appreciative of those firms whose commercial announcements are printed in this publication, and which permit the publishers to issue this Journal in its present size and its unusually attractive format. Whenever possible, readers should go out of their way to use or to recommend the excellent products which our advertisers submit. They announce the best; the best should be none too good for patients and for office and hospital exhibition.

F. S.

## ABANDONING FREE REPRINTS

IN the attempted economic "comeback," one of the Administration's pet projects has been the raising of prices. Far be it from us to question the wisdom or the necessity of such course. We leave decisions of this kind to those at present in authority.

While the general increase in costs to the public may put into circulation greater amounts of money and this manoeuvre may enable manufacturers to pay higher wages and retailers to secure greater dollar-profits, yet, it cannot be denied that, in the workings of the mechanism whereby prices to the consumer are raised, certain groups suffer.

One of the classes upon whom is imposed an onerous burden, is the magazine publisher—particularly, he who issues a scientific publication. Verily, he is "between the devil and the deep sea": he finds it impossible to raise his annual subscription-rate or the charges which he makes to his advertisers, yet his publishing costs—paper, illustrations, labor, printing—all step up briskly. As a consequence, he is compelled to "cut corners" in every conceivable fashion.

This Journal has been affected as have others. It has endeavored in no way to "economize" through cheapening its product. Its paper, style, make up, printing of elaborate tables, graphs, photographic reproductions—all have remained uncurtailed. But the management no longer is able to supply authors with the customary fifty *gratis* reprints.

Of course, many of our leading medical journals never have granted free reprints and do not do so at

present. However it had been the desire of this Journal to make at least a gesture of appreciation of the efforts of its contributors and present them with reprints sufficient to enable them to circulate the results of their studies among interested friends and colleagues. That the Journal no longer is able to help this laudable purpose assumes the significance of a major sorrow. We trust that our contributors will understand our regret and will appreciate our position.

Parenthetically, it may be mentioned that the issuance of reprints—paid for or *gratis*—imposes a considerable burden upon magazine publishers. In pride at seeing his work in type and in the exuberance consequent upon a job well-done, not rarely an author orders great numbers of reprints. His intentions are entirely understandable to publishers. However, by the time the publisher furnishes the reprints, not uncommonly, the contributor has become engrossed with other tasks to a degree where his check-writing arm has become weakened or wholly inert: as a result, this and other publications, each month lose hundreds of dollars because contributors fail to remember to remit for reprints supplied to them at cost. When they do not pay, the publisher has to foot the bill!

We shall appreciate all possible help in solving this reprint problem. Our contributors can depend upon the publishers again furnishing a number of reprints *gratis* just so soon as economic conditions make such course possible.

F. S.

## SECTION IX—Book Reviews

(This section is open to contributions from any medical reader, whether a member of the Editorial Council or not).

★★★★ "Physiology in Modern Medicine," J. J. R. Macleod, M.B., LL.D., D.Sc., F.R.C.P., F.R.S., Regius Professor of Physiology in the University of Aberdeen, Scotland, etc., with the collaboration of Philip Bard, Edward P. Carter, J. M. D. Olmsted, J. M. Peterson, and N. B. Taylor; published by the C. V. Mosby Company, St. Louis, Mo., 1935.

This substantial, inclusive, and inspiring volume of 1154 pages is the seventh edition of a textbook which has enjoyed great popularity since the first edition appeared in 1918. The word "biochemistry" has been removed from the title, and chemical subject-matter has been included "only so far as is necessary to the elucidation of the problems of animal function."

The work of the five collaborators has made it possible to give the work a completeness and up-to-date-ness which would be impossible for one man to attain, in this day and age. The final editing has been so smoothly done that there is no suggestion of the incoherence and repetition which occasionally mar such work. There are 297 figures, 7 of them in color. The table of contents and the index are both good, and the bibliography deserves the highest commendation.

Going through the table of contents, your reviewer was surprised by the absence of a section on reproduction. A few years ago it was customary to lament the fact that the chief source of information on this subject available to most people was gossip and popular jests. At present the situation is not so much better as one might expect. Suppose that one wishes to know whether a given troublesome symptom in a woman may be a normal incident to her menopause, or that one wishes to refer an intelligent patient to a book in which she will find a description of what to expect during this worrisome period. If one goes to the textbook of gynecology that is most popular among students here at present, one finds, not a connected account of the normal menopause, but scattered items amid a mass of pathological and surgical discussion. Suppose that one wishes to know whether in this climate it is normal for a boy of 12 to have erotic dreams with emissions. If one goes to the two textbooks of urology most popular here at present, one discovers that the first does not even contain the word "puberty" in its index; the other book has it, but is so filled with misleading, antiquated verbiage about "solitary vice" and "involuntary pollution" that it reads like something out of the nineteenth century. If one goes to a

textbook of psychology one may find a pitiful, shrinking nucleus of normal facts so surrounded by a spongioplasm of the speculative and the abnormal that layman and physician alike are repelled.

Surely, then, the physiologist must assume more responsibility than merely "to ascertain to what extent the known laws of physics and chemistry explain the phenomena of life." He has the further responsibility,—indeed, it might be considered his *first* responsibility—of describing and defining, for the clinician and his patients, the normal function of everything in the body. We should be able to go to him for concrete, even quantitative, statements as to the physical details of the normal human life.

The extent to which physiologists have evaded this responsibility in the past is amazing. One very well-known book of 862 pages has a section of 1¼ pages headed "Reproduction," in which the author mentions Shakespeare and Sir Thomas Browne, refers literally to the lilies of the field, and finally, gathering up all his courage, devotes the remaining half-page to parthenogenesis in the sea-urchin. In many books some of the subject-matter in question may be found under "Endocrinology," with the questions which are most urgent to the average reader left unanswered.

It seems unkind to report this defect in a book which in every other respect is magnificent. It will be found useful alike to the student, the instructor, and the medical practitioner.

Frederic T. Jung, Chicago.

"Emotions and Bodily Changes," by H. Flanders Dunbar, M.D., Ph.D., Columbia University Press, New York, N. Y., p. 595, \$5.00.

**T**HIS survey of literature on psychosomatic interrelationships covers the involved problems without omission of important contributions and without confusion of theory with fact. The integration of soma and psyche as but different manifestations of the person, develops the organismal view-point. The average 'medically trained mind' may require some reconditioning prior to acceptance of the connotation of this philosophico-physiologic trend—namely, the saturation of the tissues with soul. 'Soul' being closely related with 'purpose,' the individual cannot be intelli-

gently perceived save within a broad focus which includes his multiform and manifold relationships with environment. Equally unintelligible becomes an organ separated from its functional life or a tissue dissected from its organ. Since, up to the present, the analytic attitude and method have brought us to an obvious *impasse*, the newer method of 'wholeness' or integration may build a new structure of facts upon the fundamental theorem that the whole is more than the sum of all its parts. Psychosomatic dichotomy appears to be yielding to psychosomatic unity.

The large section on organs or organ-systems presents almost endless evidence of the primary importance of psyche in the production of somatic symptoms, as well as the reverse. This material is, of course, all very much up-to-the-minute in scope and accuracy. The subsection on the digestive tract is well handled and many outstanding gastroenterologists are extensively quoted, both American and foreign.

Dr. Dunbar's book is interesting, stimulating and practical. To medicine it brings a specific and very practical message. To psychology and psychiatry it offers much valuable correlation with the soma. In biology and philosophy the book is of monumental importance. More than 120 pages of bibliography are added for those who desire to pursue the subject further.

The integration of soma and psyche is a brave and ponderous labor projecting itself doubtless into the next few centuries. The new synthesis demanded by the current and modern intelligence in its (usually inadequate) attempt to adjust to the immensities, might grow from this root-stalk of psychosomatic integration. The purpose of the individual human has so far only the religious and philosophic explanations available, especially in so far as the psychic phase is concerned. Successfully demonstrated integration of mind and body could scarcely fail to lead to several potentially important consequences anon—a form of pantheism built on knowledge rather than faith, conservation of the energy units of psyche as well as the conservation of the energy units of organized matter. Dr. Dunbar has done much to lessen chaos within this difficult and fascinating terrain.

Beaumont S. Cornell, M.D., F.A.C.P.

## SECTION X—After “Hours”

### An Exhibition of Books Illustrating the Progress of Gastroenterology Shown at the Graduate Fortnight\*

OCTOBER 22—NOVEMBER 2, 1934

Arranged by

BURRILL B. CROHN, M.D.

and

B. D. ROSENAK, M.D.  
NEW YORK CITY, NEW YORK

**P**HYSICAL limitations of space necessitate the omission of many valuable and essential links in the history of the development of this subject. The purpose of this exhibit was to demonstrate the outstanding publications rather than to give an exhaustive display of all works. We wish to thank the Library Staff for their kind assistance in preparing the exhibition.

#### HYGIENE AND MEDICINE IN ANTIQUITY

##### BIBLE.

The Holy Bible, Conteyning the Old Testament and the New . . .

London, by Rob. Barker, 1611.

First issue of the first edition of the authorized version.

Opened at Chapter XI of Leviticus, to show dietary laws and sanitary regulations.

Kindly lent by the Union Theological Seminary.

##### JASTROW, MORRIS (1861-1921).

The Liver in Antiquity and the Beginnings of Anatomy.

In: Tr. Coll. Physicians of Phila. 3. ser. 29 :117-138, 1907.

Anatomy began in antiquity with the study of this organ, regarded at that time as the seat of the soul and of life. It was the organ most carefully scrutinized as a means of divining the future, of exorcizing evil, and of forestalling misfortune.

Opened at p. 126. Excellent clay models of the liver exist dating back as far as 2000 B.C. (Babylonian period of Hammurabi). The lobes of the liver were studied and the position of the fissures and of the gall bladder noted.

##### HIPPOCRATES (b. ca. 460 B. C.).

Cinquieme livre des epidemies. In his: Oeuvres completes . . . Traduction nouvelle . . . par E. Littré.

Paris, Bailliere, 1839-1861, vol. 5, pp. 198-259.

Opened at pp. 206-207. Case 6 is probably a clinical description of a gastric or duodenal ulcer with a spontaneous remission or healing. This short clinical note is a characteristic example of the ability of the first great physician to observe, to correlate and succinctly to describe.

\*Published through the courtesy of the Officers and Committees of the New York Academy of Medicine. Only a partial list is published herewith.

Submitted February 12, 1935.

##### GALEN (ca. 129-200).

De Naturalibus Facultatibus . . . In his: Opera ex Nona Juntarum Editione . . .

Venetis, apud Juntas, 1625, vol. 1, ff. 289/90-308.

Galen is the outstanding representative of Roman medicine or rather of Greek medicine in Rome. He was an ardent admirer of Hippocrates, but scoffed at the Alexandrians and subsequent schools. His was the dominant influence throughout mediaeval and monastic medicine.

Book III, p. 303 is an excellent example of Galen's knowledge of a gastro-intestinal subject. He is lacking in the underlying understanding of anatomy and physiology, yet he is practical, logical and reasonable in his handling of the subject.

On the Natural Faculties, with an English Translation by Arthur John Brock.

London, Heinemann, 1916.

Opened at p. 237: "Thus the two faculties are clearly to be seen in the case of the uterus; in the case of the stomach they appear as follows:—Firstly in the condition of gurgling, which physicians are persuaded, and with reason, to be a symptom of weakness of the stomach; for sometimes when the very smallest quantity of food has been ingested this does not occur, owing to the fact that the stomach is contracting accurately upon the food and constricting it at every point; sometimes when the stomach is full the gurglings yet make themselves heard as though it were empty. For if it be in a natural condition, employing its contractile faculty in the ordinary way, then, even if its contents be very small, it grasps the whole of them and does not leave any empty space. When it is weak, however, being unable to lay hold of its contents accurately, it produces a certain amount of vacant space, and allows the liquid contents to flow about in different directions in accordance with its changes of shape, and so to produce gurglings."

##### EARLY CLINICAL MEDICINE AND RENAISSANCE ANATOMISTS ARETAEUS (Cappadox) (Second to third century, A. D.)

On the Causes and Symptoms of Chronic Diseases. In his: Extant works . . . edited and translated by Francis Adams.

London, Sydenham Society, 1856, Book II, pp. 291-373.

Little is known of the life of Aretaeus. He was a contemporary of Galen, but it is only in more modern times

that he has been appreciated as the clinician of his period ranking next to Hippocrates.

Opened at p. 353, at section on dysentery, remarkable in its perfect description of the clinical features and pathological picture of instances of ulcerative colitis or dysentery. It is quite obvious that Aretaeus dissected his post-mortem material.

AVICENNA (980-1037).

Canon de Medicina. Lib. I-V. Translated by Gerardus Cremonensis.

Venice, Petrus Maufer et socii, 1486.

The translations which follow are taken from: Gruner, O. C. A Treatise on the Canon of Medicine of Avicenna. London, Luzac, 1930.

"The standard size of the meal depends on usage and vigor. A normally robust person should take as much as will not produce a sense of heaviness, or a sense of tightness of the hypochondria. There should be no subsequent rumbling in the stomach, or splashing of the food on bodily movement. Nausea should not be experienced, nor a canine appetite, nor loss of appetite, nor great disinclination for exertion, nor sleeplessness. The taste of the food should not repeat in the cructations. If the taste of the food lingers in the mouth a very long time after the meal, it shows that the latter was too heavy.

"A person who cannot digest the amount of food appropriate for him should increase the number of articles of diet, but diminish the quantity.

"A person of atrabilious constitution needs a diet which is very humectant but not very heating.

"A person of choleric constitution needs a diet which is humectant and infrigidant.

"A person who generates hot inflammable blood needs feebly nutritious articles of food, which are cold. One who generates phlegmatic blood needs feebly nutritious articles of diet which are hot and attenuant."

MUNDINUS (ca. 1275-1350).

Anatomia. Edited by Martinus Pollich de Mellerstat.

[Leipzig, Martin Landsberg, ca. 1493].

Mundinus, the son of an apothecary, was born in Bologna. The mediaeval revival of human dissecting centers around him. This little treatise of systematic anatomy based on the dissection of autopsy material was the most important anatomical work in the medical schools until superseded by Vesalius' *Fabrica*.

Opened at f. Biv to show sections dealing with the anatomy of the duodenum, mesentery and stomach. A translation of this portion follows. "And it is said that the first intestine is called the duodenum because its length generally is twelve fingers. And a certain intestinal duct from the gall bladder joins this, and for that reason be careful when you dissect not to cut this duct: but cut the intestine well below the duodenum and ligate it and then begin as classical authors began. You have six intestines. The first is the duodenum, the second the jejunum, the third the ileum, and these are slender and placed superficially. The fourth is the caecum, the fifth is the colon and the sixth is the rectum. All these intestines you will see to be rolled up and continuous and attached dorsally, just as all viscera are attached by a certain part which is called *encuras* or rather the mesentery from the mesenteric [veins] which are in it, and the Bolognese call it colloquially the *interum* as it holds up the intestines."

DA VINCI, LEONARDO (1452-1518).

I Manoscritti . . .

Torino, Roux e Viarengo, 1901. Fogli B, Dell'anatomia.

The greatest artist and scientist of the Italian Renaissance. He made over fifty careful and accurate human dissections, years before Vesalius, and drew the muscles and skeleton with great accuracy. He was also interested in the thoracic and abdominal viscera.

Opened to plate preceding p. 99.

This illustration of the thoracic and abdominal cavity shows the oesophagus as a straight tube joining the mouth cavity and the stomach. The intestinal coils he represents in several different forms, but fails to recognize the constant curve of the duodenum. The colon is fairly accurately represented and the appendix is shown.

The notes are in "mirror writing."

VESALIUS, ANDREAS (1514-1564).

De Humani Corporis Fabrica Libri Septem.

Basileae, ex off. J. Oporini, 1543.

This masterpiece of Vesalius was the culmination of many years of dissection and teaching of anatomy. It is divided into seven books and is beautifully illustrated by Jan Kalkar, a pupil of Titian. It has never been completely translated. Vesalius has been called "The Reformer of Anatomy" and his book completely disposed of Galenical anatomy.

Opened at p. 365.

Book V is devoted to the abdominal viscera. The omentum and the general disposition of large and small bowel are illustrated and described. The vermiform appendix is portrayed, and described in the text. The "mesenteric gland" or pancreas is described, but the stomach, liver, spleen and kidneys are inadequately portrayed.

#### 17TH CENTURY ANATOMISTS

ASELLIUS, GASPAR (1581-1626).

De Lactibus . . .

Mediolani, apud J. B. Bidellum, 1627.

One of the post-Vesalian anatomists, Aselli was the first to oppose the Galenic idea that chyle passed directly through the mesenteric veins to the liver. It is said by some that he did not actually see the lacteals, merely inferring their existence. He nevertheless expounded strongly on this subject and subsequent anatomists substantiated his teaching.

His original striking colored woodcuts constitute the first use of this medium in anatomical illustration.

GLISSON, FRANCIS (1597-1677).

Anatomia Hepatis.

Londini, typ. Du-Gardianis, 1654.

Famed as anatomist, physiologist and pathologist. His most important contribution was an accurate description of the capsule of the liver as well as of its blood supply. He was a graduate of Cambridge and was for many years Professor of Physic at his Alma Mater. He was one of the founders of the Royal Society.

Opened at pp. 146-147: description of bile duct.

WIRSUNG, JOHANN GEORG (d. 1643).

Figura ductus cuiusdam cum multiplicibus suis ramulis noniter in Pancreate . . . in diuersis corporibus humanis obseruati.

Paduae, 1642.

Wirsung, a prosector in anatomy at Padua during Vesling's time, discovered and described the pancreatic duct. The original plate showing this study is exceedingly rare, having been published as a single small oblong folio. Vesling incorporated this fact in his subsequent editions, giving the credit to Wirsung for the discovery. The plate shown was that reproduced in Ludwig Choulant's *History and Bibliography of Anatomic Illustration*, Chicago, Chicago University Press, [1920], p. 244.

WHARTON, THOMAS (1614-1673).

Adenographia, sive Glandularum Totius Corporis Descriptio . . .

Londini, J. G. imp. authoris, 1656.

One of a great group of 17th century anatomists. In this book, the first edition of which is shown, the various glands are described in greater detail than by previous authors.

Opened at pp. 132-133, to show illustration of duct of submaxillary gland.

STENON, NICOLAUS (STENSEN, NIELS) (1638-1686).

*Observationes Anatomicae.*

Lugd. Batav., P. de Graaf, 1680.

A priest and physician and an accomplished man in many fields: anatomy, physiology, geology and religion. In 1661 he discovered the duct of the parotid gland in the sheep and this discovery was published in his *Observationes anatomicae* in Leyden in 1662.

Opened to show illustrations opposite p. 37, of the duct of the parotid gland in sheep.

HENLE, FRIEDERICH GUSTAV JACOB (1809-1885).

*Symbole ad Anatomiam Villorum Intestinalium. . .*

Berolini, A. Hirschwald, 1837.

One of the greatest histologists of his time and one of the most eminent contributors to anatomy of all time. His outstanding contribution to gastroenterology was the accurate description of the epithelium of the intestines and identification of the intestinal villi. The lymph vessels of the villi were recognized and their communication with the blood vessels of the mesentery was noted.

Opened at p. 37, to explanation of illustrations of epithelium of intestines. Illustration unfolded for view.

#### CHEMICAL PHYSIOLOGY

VAN HELMONT, JOANNES BAPTISTA (1577-1644).

*Ortus Medicinae. . .*

Amsterdam, apud L. Elzevirium, 1648.

A disciple of Paracelsus, van Helmont maintained the idea of "archaeus," the guiding spirit of all material processes. He observed the production of "gas" in the numerous chemical processes characteristic of "fermentations." This gas was a spirit liberated from various substances by the action of fermentation. Gastric digestion began in the stomach as a "fermentation" process which turned food into chyle. Further fermentation or chemical change occurred in the intestinal tract and transformed chyle into "erude blood," thence to the liver as "vital blood" and returned to the heart as the vital spirit or "archaeus."

Opened at pp. 202-203.

van Helmont considered gastric juice to be "acid."

DE GRAAF, REINIER (1641-1673).

*De Suceo Pancreatico.* In his: *Opera Omnia.*

Lugd. Batav., Ex officina Hackiana, 1677, pp. 491-566.

de Graaf was a pupil of Franciscus Sylvius, and at the age of 23 made an investigation of the pancreatic juice, first published in Leyden in 1664. Using a quill as a cannula he examined the secretions of the pancreatic duct in a dog and determined, chiefly by taste, that the juice was "acid." He thought that bile and pancreatic juice mixed and effervesced in the duodenum.

Opened at p. 505: chapter on pancreatic juice. This is the first attempt at experimental physiology in medical literature.

DE REAUMUR, RENE ANTOINE FERCHAULT (1683-1757).

*Sur la digestion des oiseaux.*

In: *Mem. Acad. ray. d. sc.*, pp. 266-495, 1752.

The investigations of Reaumur were extremely diverse. He was the author of a great work on insects, and was the inventor of the thermometer which bears his name.

In his work on the digestion of birds he utilized the well-known habit of kites of rejecting particles which they could not digest and fed them wire mesh capsules in which portions of food were placed. He studied the solvent action of the gastric juice on these rejected foods and calculated that "putrefaction played no part in gastric digestion," thus refuting van Helmont and Sylvius.

YOUNG, JOHN RICHARDSON (1782-1804).

*An experimental Inquiry into the Principles of Nutrition and the Digestive Process.*

[Phila., T. & W. Bradford, 1805.]

This study was the graduating thesis of the young student at the University of Pennsylvania. In it he demonstrated that the flow of gastric juice and of saliva are associated and synchronous. He inferred that the acidity of the gastric secretion was due to phosphoric acid, a misconception corrected shortly after (1825) by Prout.

PROUT, WILLIAM (1785-1850).

*On the Nature of the Acid and Saline Matters Usually Existing in the Stomachs of Animals.*

In: *Phil. Tr.*, Lond., 1824, pp. 45-49.

The first English physiological chemist and distinguished in this field by his discovery that the stomach contains free hydrochloric acid.

#### EXPERIMENTAL PHYSIOLOGY

MAGENDIE, FRANCOIS (1783-1855).

*Memoire sur le vomissement.*

Paris, Crochard, 1813.

The pioneer experimental physiologist of France, he was an ardent defender of animal experimentation and the founder of modern experimental pharmacology and demonstrated the action of many drugs, which he introduced into medical practice. His contributions are numerous, though Garrison says of him: "He discovered only isolated facts, did not try to connect them with one another by any special hypothesis, and so arrived at no important generalizations." He was the teacher of an illustrious pupil, Claude Bernard.

He made important investigations into the mechanism of deglutition and vomiting.

BEAUMONT, WILLIAM (1785-1853).

*Experiments and Observations on the Gastric Juice.*

Plattsburgh, Allen, 1833.

The unique accident which made possible the far-famed observations on the digestive processes in man is herein described. A Canadian half-breed, Alexis St. Martin, sustained a gunshot wound of the abdomen. He survived, but with a gastric fistula. Beaumont availed himself of this unusual opportunity to make the most significant contribution to gastric physiology prior to Pavlov. He found that digestive juices were secreted only when there was food in the stomach and that simple irritation of the mucous membrane would not initiate a flow of gastric juice. He studied the digestibility of various foods, the influence of emotions, of work and of illnesses upon gastric secretion and digestion.

BERNARD, CLAUDE (1813-1878).

*Du suc pancreatique et de son role dans les phenomenes de la digestion.*

In: *Arch. gen. de med.* 4 ser. 19 :60-81, 1849.

Trained in his youth by the Jesuits, Claude Bernard was a pharmacist and a playwright before turning to the pursuit of medicine. He was a pupil of Magendie and his natural talents as a pioneer in experimental physiology made possible his numerous contributions in that field.

His greatest gift to gastro-intestinal physiology was his work on the pancreatic juice (1849-1856), in which he showed the effect of the pancreatic secretion in emulsifying fats and in converting starches into sugars, also its solvent action on proteins.

KUHNE, WILLY (1837-1900).

*Ueber das Trypsin (Enzym des Pankreas).*

In: *Verhandl. d. naturhist.-med. Vereins zu Heidelberg*, (1876), n. F. 1 :194-198, 1877.

Kühne was a pupil of Claude Bernard and was Professor of Physiology both in Amsterdam and in Heidelberg. His chief contributions to gastro-intestinal physiology are his *chemical studies of the intermediate digestion of proteins* and his discovery of the proteolytic enzyme in pancreatic juice, which he called "trypsin."



PAVLOV, IVAN PETROVICH (1849- ).

The Work of the Digestive Glands. 2. English ed.  
London, Griffen, 1910.

Pavlov, the son of a Russian priest, was a pupil of Heidenhain and of Ludwig. From the former he learned the technique of animal surgery and acquired an extraordinary ambidexterity. He was the founder of an eminent school of experimental physiologists.

Opened at pp. 16-17.

Illustration of his gastric pouch. By feeding a dog with such a pouch he was able to demonstrate "psychical secretion" of gastric juice. He showed that section of splanchnic nerves had no effect whereas section of the vagi would stop reflex gastric secretion.

He also studied pancreatic secretion and observed that pancreatic juice was activated by a duodenal substance which he named "enterokinase."

CANNON, WALTER BRADFORD (1871- ).

The Movement of the Stomach Studied by Means of the Roentgen Rays.

In: Am. J. Physiol. 1 :369-382, 1898.

Cannon conceived the idea of studying the movements of the gastro-intestinal tract in animals experimentally by means of the x-ray, utilizing bismuth subnitrate as an opaque medium.

Opened at pp. 370-371. Plate demonstrating the original tracings of the stomach of the cat at successive intervals following a bismuth meal.

#### HISTORY OF THE STOMACH TUBE

HUNTER, JOHN (1728-1793).

A case of Paralysis of the Muscles of Deglutition Cured by an Artificial Mode of Conveying Food and Medicine into the Stomach.

In: Tr. Soc. for Improvement of Med. & Chir. Knowledge, Lond., 1 :182-188, 1793.

Hunter came to London in 1748 and studied anatomy under his brother William, and surgery under Cheselden and Pott. He is considered the founder of experimental and surgical anatomy. He has been hitherto regarded as the first to introduce artificial feeding through a flexible tube passed into the stomach, but there is now good evidence that Alexander Monro (secundus) employed this method prior to Hunter's time.

MONRO, ALEXANDER (secundus) (1733-1817).

Operations in Surgery (manuscript notes of a student), 1775-1790.

Monro was a member of the famous family of surgeons and anatomists whose lives are so closely connected with the development of the Medical School of the University of Edinburgh. He succeeded his father as Professor of Anatomy and Surgery there and lectured between 1759 and 1800.

The manuscript here presented is in the hand of Samuel Davidson, who was a pupil of Monro between 1775 and 1790. These notes, taken at Monro's lectures, contain a description of a disease of the oesophagus with constriction and narrowing, as well as a symptom complex closely resembling cardiospasm.

For these conditions Monro recommended the passage of bougies, and suggested that by passing a hollow flexible tube, the purpose of the bougie and a means of feeding the patient would be provided by one instrument.

LARREY, DOMINIQUE JEAN (BARON) (1766-1842).

Memoires de chirurgie militaire et campagnes.

Paris, J. Smith, 1812.

Baron Larrey, the greatest French military surgeon of his time and a favorite of Napoleon during his campaigns,

devised many operations and contributed much to military surgery.

He was the first to use intubation of the oesophagus in cases of gunshot wounds, devising the method as a means of feeding the famous Marshal, Baron Desault, who was suffering from paralysis of the oesophageal muscles as a result of a penetrating bullet wound.

JUKES, EDWARD (fl. 1822).

New Means of Extracting Opium, &c. from the Stomach.

In: London M. & Phys. J. 47 :384-389, 1822.

Jukes and Francis Bush wrote simultaneously on the subject of lavaging the stomach by means of a hollow flexible gum tube in cases of opium poisoning. Neither writer knew of the work of the other, nor did they know that Physick, an American (1800) had utilized intubation in a very similar manner.

A letter by Bush: "On removing opium from the stomach with a syringe" will be found on p. 541 of this journal.

EWALD, CARL ANTON (1845-1915).

Beitrage zur Physiologie und Pathologie der Verdauung.

In: Virchow's Arch. 101 :325-375, 1885.

Ewald was an assistant to Frerichs and was Senator's successor at the Kaiserin Augusta Hospital. He is known for his valuable contributions to the knowledge of disorders of digestion. He published his work on intubation for examination of the stomach in 1875, and in conjunction with Boas, his description of the "test breakfast" in 1885. This simple meal of bread and tea became the standard test meal and is still in universal use.

EINHORN, MAX (1862- ).

Die neueren Methoden der Magenuntersuchungen.

Reprinted from: New Yorker med. Monatsschr. 1 :113-122, 1889.

Einhorn was a graduate of the University of Berlin and later became a practitioner and teacher in New York. He was the inventor of many ingenious diagnostic devices, among them the stomach bucket, in 1890, and the duodenal bucket, in 1908.

#### CLASSICAL DESCRIPTIONS OF GASTRIC ULCER

DONATUS, MARCELLUS (LATTER HALF OF 16TH CENTURY).

De Historia Medica Mirabili Libri Sex.

Francofurti ad Moenum, impensis J. J. Porsii, 1613.

Donatus studied medicine at Padua. He practiced in Venice and later went to Mantua, where he became Secretary of State and was made a Count.

He published in Mantua in 1586 his *De Historia Medica*, in which is found the earliest known report of a gastric ulcer discovered at autopsy. The edition here shown is the one published in Frankfurt after his death. Opened at pp. 308-309.

BAILLIE, MATTHEW (1761-1823).

The Morbid Anatomy of Some of the Most Important Parts of the Human Body. 2. ed.

Lond., J. Johnson, 1797.

Baillie was urged to study medicine by his uncle, the celebrated William Hunter, and became a pupil of Hunter and of Morgagni. He was an eminent practitioner in London, as well as an astute student of pathology. His works show a systematic attempt to correlate pathology and clinical medicine.

In the book exhibited, which was first published in 1793, he gives the first clear description of the morbid anatomy and the clinical symptoms of gastric ulcer.

Opened at pp. 140-141.

**ABERCROMBIE, JOHN (1780-1844).**

Pathological and Practical Researches on Diseases of the Stomach, the Intestinal Canal, the Liver, and other Viscera of the Abdomen.

Edinb., Waugh & Innes, 1828.

Abercrombie received his doctor's degree at Edinburgh in 1803 and after spending a year in further study at St. George's Hospital, London, returned to Edinburgh to practice. He kept with scrupulous care a record of every case of scientific interest that came before him and many of these observations are incorporated in his two principal works.

Opened at pp. 34-35 showing a description of a case of gastric ulcer, in which the symptoms of perforation and hemorrhage are noted and excellent recommendations concerning treatment are made.

**CRUVEILHIER, JEAN (1791-1874).**

Maladies de l'estomac. In his: Anatomie pathologique du corps humain.

Paris, Bailliere, 1835-42, Vol. 2.

Cruveilhier graduated in 1816 from the University of Paris, where he was a pupil of Dupuytren. He returned to Limoges to practice, but was persuaded to return to Paris as Professor of Pathology.

His *Anatomie pathologique du corps humain* is a remarkably illustrated atlas of gross pathology. Plates showing ulcers of the stomach are here shown. It is often claimed that his was the first pathologic description and depiction of gastric ulcer, and the name "Cruveilhier's ulcer" was much in use in France. However, he was preceded by Abercrombie and Matthew Baillie. Cruveilhier is rightly credited with the differentiation of benign gastric ulcer and carcinoma, but microscopic studies are lacking.

**DIEULAFOY, GEORGES (1839-1911).**

Exulceratio simplex, diagnostic anatomique et diagnostic clinique.

In his: Clinique medicale de l'Hotel-Dieu de Paris, 2 :23-62, 1897-98.

Dieulafoy was a distinguished practitioner of Paris but although an alert and intelligent physician and an excellent teacher he was not a profound scientific investigator. His work on internal medicine was very readable and popular.

He differentiated acute gastric ulcer which he called "exulceratio simplex" from chronic gastric ulcer, "ulcus simplex" of Cruveilhier. He advanced a toxi-infectious theory of the etiology of acute ulcers and thought that they were the precursors of chronic ulcers. Among his case reports are instances of fatal gastric hemorrhage from acute gastric ulceration at the fundus.

**DUODENAL ULCER; TYPHOID AND TYPHUS FEVERS  
PATHOLOGICAL ANATOMY**

**HAMBERGER, GEORGIUS ERHARDUS (1697-1755).**

De Ruptura Intestini Duodeni.

Jenae, lit. Ritterianis, [1746].

Hamberger received his doctor's degree at Jena in 1721 and was later Professor of Chemistry, and practiced at that University.

He described, in 1746, the case of a young woman who, after gathering plums in the morning, was seized with violent abdominal pains and died in a short time. Upon opening the abdomen post-mortem Hamberger found gas, fluid, and in the duodenum a perforation the size of a pea. This is probably the first reported case of a *perforated duodenal ulcer*.

**MOYNIHAN, BERKELEY GEORGE ANDREW MOYNIHAN, 1ST BARON (1865- ).**

On Duodenal Ulcer and its Surgical Treatment.

In: Lancet, 2 :1656-1663, 1901.

a military surgeon. His contributions to abdominal surgery are numerous and important.

His great pioneer work in surgery was his account of the characteristics and symptoms and surgical treatment of duodenal ulcer. Isolated pathological reports of this condition had occasionally been noted and been lost in obscure literature but its occurrence, remarkable frequency, and clinical characteristics were first adequately described by this author.

**BRETONNEAU, PIERRE (1778-1862).**

Notice sur la contagion de la dothineritric; luc a l'Academie Boyale de Medecine, le 7 juillet 1829.

In: Arch. gen. de med. 21 :57-78, 1829.

Bretonneau wrote on typhoid fever in 1829, describing at that time the lesions in Peyer's patches. He also anticipated the differentiation of typhoid and typhus fevers and was an early supporter of the germ theory of disease.

**LOUIS, PIERRE CHARLES ALEXANDRE (1787-1872).**

Recherches anatomiques, pathologiques et therapeutiques sur la maladie connue sous les noms de gastro-enterite, fièvre putride, adynamique, ataxique, typhoide. . . Paris, Bailliere, 1829.

This is the first time that the name *typhoid* fever rather than *dothineritis* was applied to this disease.

Louis was famous as a teacher of American physicians. Through his influence on such men as O. W. Holmes, the Shattucks, Gerhard and others, he extended a dominating influence upon medicine in the United States.

**MORGAGNI, GIOVANNI BATTISTA (1682-1771).**

De Sedibus et Causis Morborum. . .

Venetis, ex typ. Remondiniana, 1761. 2 vols. in one.

Morgagni received his medical education at Bologna and was much influenced by his teacher, Valsalva. At the age of 29 he was called to Padua as Professor of Surgery to fill the chair once occupied by Vesalius. His life was spent apart from the affairs of the world in indefatigable labors in dissection, clinical consultations and teaching, with no thought of self interest or renown.

The works of Morgagni were not published until his seventy-ninth year, when they appeared in the form of five books of informal letters. This work constitutes the foundation of modern pathologic anatomy, bringing about for the first time a systematic correlation of clinical data and post-mortem findings. He was the first to describe the clinical and pathologic features of acute yellow atrophy of the liver. In 1733 Morgagni described a case of duodenal ulcer complicating ulcers of the stomach.

This book is opened at vol. 2, p. 73, to a section in which this very astute clinician and pathologist describes and discusses a case of "emotional jaundice."

**BRIGHT, RICHARD (1789-1858).**

Cases and Observations Connected with Disease of the Pancreas and Duodenum.

In: Med.-Chir. Tr., Lond., 18 :1-56, 1833.

Bright was a pupil of Sir Astley Paston Cooper. He was physician to Guy's Hospital for 23 years and the ward where he made his rounds still bears his name. The leading consultant of London in his time, he was known for his dissection of autopsy material as well as for the practice of clinical medicine.

He described essential nephritis and first differentiated between cardiac and renal dropsy. In the field of gastroenterology his clinical descriptions and pathologic studies in pancreatitis and diabetes are classic gems of medical literature.

Account of a Remarkable Misplacement of the Stomach.

In: Guy's Hosp. Rep., 1:598-603, 1836.

The first pathological and clinical description of a congenital thoracic stomach. Clinical knowledge of this remarkable condition is just appearing in very

MEGACOLON; CONGENITAL PYLORIC STENOSIS;  
APPENDICITIS

RUYSCH, FREDERICUS (1638-1731).

Observationum Anatomico-chirurgicarum Centuria.

In his: Opera Omnia, Amstelodami, apud Janssonio-Waesbergio, 1737, vol. 1, 86.

A pupil of Sylvius, Ruysch, like the physicians of his time, had wide interests such as botany, chemistry, numismatics. He was primarily an anatomist and pathologist; his name is associated with the practice of injecting arteries with colored wax and he is remembered for the excellence of his anatomical illustrations.

Observatio XCII. *Enormis intestini coli dilatatio*. Ruysch was probably the first to report (1691) the findings of an enormous dilatation of the colon in a girl fifteen years of age. The specimen is apparently one of "idiopathic congenital dilatation of the colon" described clinically, *de novo*, almost 200 years later by Hirschsprung.

HIRSCHSPRUNG, HARALD (1831-1916).

Stuhltragheit Neugeborener in Folge von Dilatation und Hypertrophie des Colons.

In: Jahrb. f. Kinderh. 27 :1-7, 1888.

Hirschsprung was Chief of Staff of the Children's Hospital of Copenhagen from 1870. Besides his original description of *dilatation and hypertrophy of the colon in the newborn*, he published papers on congenital occlusion of the oesophagus and of the duodenum, acute rachitis, rheumatic myositis in children, etc.

LEWITT, WILLIAM (fl. 1867).

Enlargement of the Colon.

In: Chicago M. J., 24 :359-361, 1867.

William Lewitt, otherwise unknown in American medicine, was the first American to describe, in 1867, a case of congenital dilatation of the colon, with clinical features and post-mortem studies. This publication antedates that of Hirschsprung by almost 20 years. Lewitt was at that time a demonstrator in Anatomy at Rush Medical College, but no further biographical data are available.

WILKS, SIR SAMUEL (1824-1911).

Lectures on Pathological Anatomy.

London, Longman, 1859.

These studies are the result of a life devoted to clinical medicine and clinical pathology at Guy's Hospital. Among the many brilliant and original descriptions in this volume is one of a type of ulceration of the colon which had hitherto not been differentiated from dysentery or similarly identified forms of colitis. Wilks is here undoubtedly describing a specimen of *severe ulcerative colitis* of the type today classed as "non-specific."

Opened at p. 301.

FERNELIUS AMBIANUS, JOANNES (1497-1558).

Universa medicina.

Francofurti ad Moenum, apud A. Wechelum, 1577.

Fernel, besides being famed as a medical practitioner, was active in many fields of research, being the first to measure accurately a degree at the meridian.

Opened at Book VI, p. 218.

The accompanying selection from his *Universa Medicina* is probably the first description of acute appendicitis with perforation. The only doubt hinges on whether the terms *caecum intestinum* refers to the caecum or the appendix, as anatomists of that time used the term to apply to both structures.

PARKINSON, JAMES (1755-1824).

Case of Diseased Appendix Vermiformis.

In: Med.-Chir. Tr., Lond., 3 :57-58, 1816.

Parkinson was the son of a physician and one of a cultured and educated family. Little is known of his education, but he was engaged in practice in 1785 and attended John Hunter's lectures in surgery during that year. He will be remembered in the main for his classical description of paralysis agitans. He was also a reformer and

political agitator. One of the early classical descriptions of appendicitis, the first one in English, is written by this author. He recognized perforation as the cause of death in this condition.

FITZ, REGINALD HEBER (1843-1913).

Perforating Inflammation of the Vermiform Appendix, with Special Reference to its Early Diagnosis and Treatment.

In: Boston M. &amp; S. J., 115 :13, 1886.

Fitz received his degree at Harvard in 1868. He spent two years abroad with Rokitsky, Oppolzer and Skoda in Vienna, and with Cornil in Paris. He found his greatest inspiration in Virchow, whose theory of cellular pathology he introduced into the United States. In 1870 he returned to Boston and led an active life in practice and teaching. This classical article on appendicitis was presented before the Association of American Physicians in 1886. Here was expounded for the first time a clear picture of the clinical course and diagnostic signs of appendicitis, together with its pathologic changes. Fitz advocated immediate operation as the only rational means of saving life.

## ABDOMINAL SURGERY

BOBBS, JOHN STOUGH (1809-1870).

A Case of Lithotomy of the Gall Bladder.

In: Indiana M. J., 18 :177-180, 1899.

Bobbs, a pioneer surgeon of Indiana, read medicine with Martin Luther of Harrisburgh, Pa. and took a course of lectures at Jefferson Medical College in Philadelphia. He soon took high rank both as a physician and surgeon. When the Medical College of Indiana was organized, he was elected Professor of Surgery and later Dean of the Faculty. The latter part of his life was devoted mainly to surgery, and as an operator he was bold and original.

He performed the first cholecystotomy in 1867. The account of it was published originally in the *Transactions of the Indiana State Medical Society* in 1868 and the above reference is a reprint, somewhat abridged.

VON VOLKMANN, RICHARD (1830-1889).

Ueber den Mastdarmkrebs und die Extirpation recti.

In: Samml. klin. Vortr. 131 (Chir. 42), 1878.

von Volkmann was the son of a well known physiologist and professor of surgery at Halle. He graduated in medicine from Berlin in 1854 and became an assistant in the surgical clinic of Blasius. He later returned to Halle to practice and to teach surgery.

He is remembered largely because of his description of ischemic contraction, but it must be noted that he was the first to perform a resection of the rectum for carcinoma in 1878.

## DEVELOPMENT OF RADIOGRAPHY

CANNON, WALTER BRADFORD (1871- ).

The Movement of the Stomach Studied by Means of the Roentgen Rays.

In: Am. J. Physiol., 1 :369-382, 1898.

This constitutes the pioneer attempt to apply the recently discovered radiographic technique to gastro-intestinal physiology. The use of bismuth subnitrate was not only a successful technical innovation, but it made possible physiological studies on peristalsis and intestinal function never before envisioned in a normal animal. (See also item no. 32.)

ROUX, JEAN CHARLES &amp; BALTHAZARD, VICTOR (1872- ).

Etude du fonctionnement moteur de l'estomac a l'aide des rayons de rontgen.

In: Arch. de physiol., 5. ser., 10 :85-94, 1898.

This article is the earliest to incorporate the idea of Cannon and to apply the bismuth contrast meal to human beings. Unfortunately the amount of bismuth subnitrate used was insufficient. This suggestion was but little improvement on the filled capsules, metal foreign bodies, coiled metal springs, and bags filled with solution of lead

acetate which were among the fantastic devices for visualizing the stomach during this initial period.

WILLIAMS, FRANCIS HENRY (1852- ).

The Roentgen Rays in Medicine and Surgery.  
N. Y., Macmillan, 1901.

Williams was educated at the Massachusetts Institute of Technology and at Harvard Medical School. He studied in Europe for two years and returned to enter general practice in 1879. He then took up the study of roentgenology to which he devoted himself thereafter. He taught X-ray diagnosis and therapy at Harvard and wrote much on the subject.

The textbook here shown, opened at p. 361, is one of the earliest in which the opaque meal was expounded as a practical mode of gastro-intestinal diagnosis. Here for the first time bismuth was used in sufficient concentration for the outline and study of the normal human stomach. This American pioneer work antedated by three years that of Rieder of Germany.

REIDER, HERMANN (1858-1932).

Radiologische Untersuchungen des Magens und Darmes beim lebenden Menschen.

In: Munchen. med. Wehnschr., 51 :1548-1551, 1904.

Studied in Vienna, Heidelberg and Munich, at which latter place he received his doctor's degree. Served on the staff of the Munich Hospital, the Medico-Clinical Institute, and under the renowned Ziemssen. He was attracted by Rontgen's discovery (1895) to such an extent that in 1901 he was already beginning to study the form and function of the alimentary tract of man by means of radio-opaque meals of bismuth. This article is the first accurate description of the radiology of the normal alimentary tract of man. It is a classic study, exact, detailed, perfect in observation.

HOLZKNECHT, GUIDO (1872-1931) & JONAS, SIEGFRIED (1874- ).

Die radiologische Diagnostik der intra- und extra-ven-trikularen Tumoren und ihre spezielle Verwertung zur Fruhdiagnose des Magencarcinomas.

Wien, Perles, 1908.

Holzknacht studied in Strassburg and Konigsberg and received his doctor's degree in Vienna in 1901. He then became an assistant in Nothnagel's clinic where he became interested in roentgenology. He studied this subject ardently for many years and was famed as a teacher and as a pioneer in the development of the clinical use of the X-ray. He was the first to devise a dosage table for X-ray therapy and did much to clarify the problems of the diagnosis of visceral disease.

His work on tumors of the stomach deals particularly with the roentgen diagnosis of carcinoma of the stomach.

COLE, LEWIS GREGORY (1874- ).

The Diagnosis of Post-pyloric (Duodenal) Ulcer by Means of Serial Radiography.

In: Tr. XVII. Internat. Cong. Med. (1913), Lond., Sect. XXII., part II (Radiology), pp. 77-81, 1914.

Cole graduated from the College of Physicians and Surgeons in 1898 and was Professor of Roentgenology at Cornell Medical College from 1913 to 1920.

A very few years after Moynihan's description of duodenal ulcer (1905), Cole's work describing the "Pileus duodeni" appeared. This pioneer work on the roentgenography of the duodenal cap remains a classic contribution.

"TWO-AND-A-HALF-FOOT SHELF" OF A GASTROENTEROLOGIST

This represented a choice of some (not all) of the modern classics considered essential to a proper understanding of gastroenterology and its relation to internal medicine. The books were chosen by one of us.

ALVAREZ, WALTER CLEMENT

Nervous indigestion.

New York, Hoeber, 1930.

ALVAREZ, WALTER CLEMENT

The mechanics of the digestive tract. 2. ed.  
New York, Hoeber, 1928.

CANNON, WALTER BRADFORD

Bodily changes in pain, hunger, fear and rage. 2. ed.  
New York, Appleton, 1929.

CANNON, WALTER BRADFORD

The mechanical factors of digestion.  
New York, Longmans, 1911.

CARLSON, ANTON JULIUS

The control of hunger in health and disease.  
Chicago, University of Chicago Press, 1916.

CARMAN, RUSSELL DANIEL

The Roentgen diagnosis of diseases of the alimentary canal. 2. ed.  
Philadelphia, Saunders, 1920.

CROHN, BURRILL B.\*

Affections of the Stomach, W. B. Saunders, 1927.

GASKELL, WALTER HOLBROOK

The involuntary nervous system.  
London, Longmans, 1916.

HURST, ARTHUR FREDERICK

Constipation and allied intestinal disorders. 2. ed.  
London, Frowde, 1919.

HURST, ARTHUR FREDERICK

The Goulstonian lectures on the sensibility of the alimentary canal.  
London, Frowde, 1911.

HURST, ARTHUR FREDERICK, AND STEWART, MATTHEW JOHN

Gastric and duodenal ulcer.  
London, Milford, 1929.

OPIE, EUGENE LINDSAY

Disease of the pancreas. 2. ed.  
Philadelphia, Lippincott, 1910.

OSLER, (SIR) WILLIAM

The principles and practice of medicine. 11. ed.  
New York, Appleton, 1930.

PAVLOV, IVAN PETROVICH

The work of the digestive glands; translated into English by W. H. Thompson. 2. ed.  
London, Griffin, 1910.

RANKIN, FRED WHARTON; BARGEN, JACOB ARNOLD, AND BUIE, LOUIS ARTHUR

The colon, rectum and anus.  
Philadelphia, Saunders, 1932.

REHFUSS, MARTIN EMIL

Diagnosis and treatment of diseases of the stomach with an introduction to practical gastro-enterology.  
Philadelphia, Saunders, 1927.

ROLLESTON, (SIR) HUMPHERY DAVY, AND MCNEE, JOHN WILLIAM

Diseases of the liver, gall-bladder and bile-ducts. 3. ed.  
London, MacMillan, 1929.

SMITHIES, FRANK, AND OCHSNER, J.

Cancer of the Stomach, W. B. Saunders, 1916.

SCHLESINGER, EMMAO

Die Rontgendiagnostik der Magen und Darmkrankheiten. 3. Aufl.  
Berlin, Urban, 1927.

TODD, THOMAS WINGATE

The clinical anatomy of the gastro-intestinal canal.  
Manchester (Eng.), University Press, 1915.

\*Editors Note: This book was omitted, apparently through modesty on the part of Dr. Crohn, but should in our opinion, be included prominently in the list.

# ABSTRACTS

JOHN R. PARRY AND KENNETH MURRAY.

*Acute Pancreatic Necrosis—a review of 20 cases.*  
*Can. Med. Assoc. Journal, Dec., 1934, p. 592-5.*

The writers think pancreatitis is probably more common than is generally supposed. The review is based on 20 cases, in which the diagnosis was confirmed by operation or necropsy. In the series there was no classical case with agonising pain, cyanosis and collapse. In most of cases, the pre-operative diagnosis was cholecystitis; and operation not urgently required. There were twice as many females as males.

Infection or exciting agents can reach the pancreas in one of 5 ways: by blood or lymph, direct extension, regurgitation from duodenum or from the bile ducts. Blood infections occur in mumps. Infection through the lymph channels from an inflamed gall bladder they think is doubtful as in none of their cases was the gall bladder very acutely diseased. Just as we get infection of the parotid from the mouth, we may get the pancreas infected from the duodenum. A case is cited of a child who 36 hours earlier had received a blow on the abdomen. At operation there were the signs of pancreatitis. The explanation offered is that a sudden increase of intra abdominal pressure caused a squirt of duodenal contents or bile into the pancreas, causing necrosis.

The pancreatic duct may terminate in one of three dif-

ferent ways. In one way, where it joins the common duct above the ampulla, it is possible for a stone to block the flow of bile into the bowel and cause it to be forced along the pancreatic duct. Again the pancreatic duct may empty in the bowel through an opening distinct from the common bile duct. In this type it would be impossible to get regurgitation from blockage of the common duct, yet in 2 of the fatal cases this was the form of termination of the pancreatic duct.

The cases showed white blood counts of 15 to 20 thousands, in the traumatic cases it was higher. Clinically pancreatitis resembles acute cholecystitis, but is more severe, and the authors believe that such a case not relieved by one or two hypodermics of morphia is likely pancreatitis. Pain and tenderness, to the left of midline and vague thickening in the epigastrium aid in making a diagnosis.

As to treatment trans-abdominal drainage is useless. Cholecystotomy is quickly carried out and will drain a likely source of infection and relieve tension. Saline and glucose intravenously are given for dehydration from vomiting and morphia for pain.

Immediate operation in the acute cases is not recommended. Removal of infected gall bladders is recommended as a prophylactic measure.

R. H. M. Hardisty, Montreal.

## SECTION XII—"The Clinic"

### Gastric Ulcer Following Duodenal Ulcer With Obstruction: Report of a Case\*

By

FRED R. HARPER, M.D.  
TUCSON, ARIZONA

THE sequence of events in this case makes it of interest even though the lesion itself is not rare.

Robertson and Hargis (1) found ulcers in both the stomach and the duodenum in twenty-seven (7 per cent) of 387 cases. In all of the 387 cases ulcers were found in either the stomach or duodenum. The cases were taken from 2000 autopsy records. Walters (2) studied the rou-

tine pathological specimens of resected stomachs from German Clinics and compared them with routine cases in this country. He concluded that gastritis and gastric ulceration associated with duodenal ulcer was much more common in Germany. He quotes Konjetzny as finding gastric changes constantly associated with duodenal ulceration. However, in a selected group of cases in which Walters did gastric resections at the Mayo Clinic, he found only two cases

in which there was gastritis or gastric ulceration. The following case is of interest because the duodenal ulcer with gastric retention was demonstrated nine months before the associated lesion was found in the stomach.

#### CASE REPORT

The patient was a male, aged 33 years. He was first seen in August, 1933. At that time he had been vomiting coffee ground material for one week. He had also had tarry stools. He

\*From the Thomas-Davis Clinic.  
Submitted April 10, 1935.

gave a history of having had epigastric pain for two years. The pain came on three or four hours after meals and was relieved by soda or vomiting, which he frequently induced for relief. Examination revealed no abnormality ex-



Fig. 1. Radiogram of stomach taken at the time of the patient's first visit. The deformity of the duodenal cap may be noted. There is no definite evidence of gastric ulceration.

## Abnormal Motility

Gastro-Intestinal symptoms may be successfully controlled by the application of

### Bile Salts Therapy



## TAUROCOL

(TOROCOL)

### Bile Salts Tablets

Increase motility, increase peristalsis, step up the flow of bile by stimulating the bile producing cells of the liver. The gradual reduced dosage of Taurocol permits of the restoration of the normal motility.

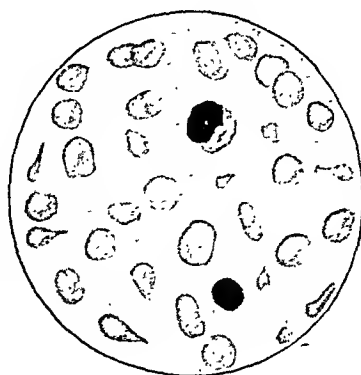
Write for sample and full information.

The Paul Plessner Co.

Detroit

Michigan

L. D. 6-35



## ANNOUNCING

### A New

## Parenteral

## Liver Extract!

Chappel's Liver Concentrate Intramuscular, for intensive treatment of pernicious anemia.

One injection per week during relapse to obtain recovery.

One injection at two to four week intervals for maintenance.

In packages of three vials. Each vial contains 3.3 c.c. derived from 150 grams of fresh liver.

Laboratories

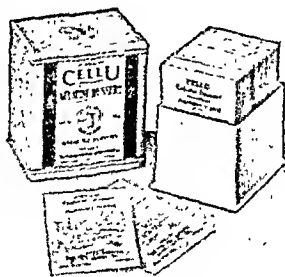
CHAPPEL BROS. INC.

Rockford, Ill.

## CELLU Gelatin Dessert

(Unsweetened)

Contains pure gelatin, true fruit flavoring, fruit acid, salt and certified color



### Food Value

The food value of one portion of Cellu Gelatin Dessert is: Protein (gelatin) 3 grams; Carbohydrate 0.24 grams; Fat none.

For Use in

## Diabetic and Ketogenic Diets

A pure unsweetened dessert powder, to which the individual may add the amount of saccharine desired when making desserts or salads.

Cellu Gelatin Dessert is made in five flavors (true fruit): Raspberry, Grape, Cherry, Orange and Lemon, and is packed 20 individual envelopes to a box. May be secured in individual flavors or in an assortment of flavors.

Send for Free Sample

Send me a Free Sample of Cellu Gelatin Dessert.



D. D. N., 6-35

CHICAGO DIETETIC SUPPLY HOUSE

1750 West Van Buren Street

Chicago, Ill.



cept for slight tenderness in the epigastrium.

Laboratory reports showed the hemoglobin to be 37%, red blood cells 2,200,000, white blood cells 8,500.

X-ray of the stomach showed marked spasm of the pylorus with a constant deformity of the duodenal bulb. The stomach did not empty in the usual 6 hours. The X-ray diagnosis was duodenal ulcer with gastric retention.

Surgery was advised but after a brief period of hospitalization the patient left against advice and was not seen again until June, 1934. For four months previous to his second visit, he had been vomiting every four or five days. For the two days previous to his return, he had vomited everything he had taken by mouth. The vomitus contained blood; he had had tarry stools.

He was found to have 1500 cc. of gastric retention. No X-ray study was

Elman and Eckert (5) have mentioned the importance of pyloric obstruction in producing increased gastric acidity. Bolton (6), in 1909, found that ulcers in cats showed delayed healing in the presence of pyloric stenosis. Friedman (7) and Hamburger produced acute ulcers with silver nitrate and caused them to become chronic by partially occluding the pylorus. Robertson and Hargis emphasized the importance of stenosis in the non-healing of peptic ulcers. Horsley (8) mentions

This journal will pay 50 cents  
each for

COPIES of the APRIL, 1935  
Issue.

Please write before sending  
the copies to The American  
Journal of DIGESTIVE DIS-  
EASES AND NUTRITION

435-455 Lincoln Bank Tower  
FORT WAYNE, IND.

## LAROSTIDIN

*"produces rapid clinical improvement . . .  
gastroduodenal ulcer . . . .  
liberal diets . . . . . ambulatory."\**



Fig. 2. Gross specimen of resected stomach showing large ulcer on the lesser curvature. The duodenal ulcer was partially crushed by the clamp.

made because of the retention. After three days of preparation with intravenous glucose, exploratory laparotomy was done. A large ulcer  $3\frac{1}{2}$  cm. in diameter surrounded by considerable gastritis was found on the lesser curvature of the stomach. There was also a definite ulcer in the duodenum.

A posterior Polya type of gastric resection was done removing about two-thirds of the stomach. The patient's convalescence has been uneventful and he is now able to eat without distress.

### COMMENT

In a recent experimental study, I (3) suggested the importance of chemical and mechanical factors in the development of peptic ulcers. Numerous other experimental studies have emphasized these factors. Steinberg and Starr (4) and also

The evidence pointing to the efficacy of Larostidin in ulcer management continues to accumulate.

In examining that evidence one finds a striking unanimity of opinion. Clinicians who have recorded their observations consider the Larostidin treatment the foremost advance in ulcer therapy. The relief, they find, is prompt. Pain, vomiting, hypersecretion, and retention quickly disappear. Appetite returns; there is a gain in weight; the entire picture changes.

According to Volini and McLaughlin\* these good results may be attributed to the decreased secretion of gastric acid—the direct result of Larostidin injections.

### HOW TO USE LAROSTIDIN 'ROCHE'

*Usual Dose:* One ampul Larostidin (5 cc.) by intramuscular injection once daily for about 24 days. . . . It is good practice to give the injections at about the same time daily and not

to skip any. Usually, about 24 injections are sufficient. Inject alternately in the arms or in gluteal muscles, preferably the latter. Inject slowly, gradually withdrawing the needle.

*Larostidin ampuls, 5 cc., cartons of 6*

**HOFFMANN • LA ROCHE • INC • NUTLEY • NEW JERSEY**

\*"The Histidine Monohydrochloride Therapy of Gastroduodenal Ulcer, VOLINI and McLAUGHLIN, *Medical Record*, April 17, 1935."

that there are some who believe that duodenal ulcer may be caused from adhesions or from pressure of the mesenteric artery on the terminal duodenum. Puhl (9) commenting on gastrojejunal ulceration says that stenosis of the stomach can lead to a diffuse and even ulcerative fundus gastritis. In view of these observations, it would seem that the duodenal ulcer and resulting stenosis may have been a factor in the etiology of the gastric lesion found in this case nine months later.

Various methods of treatment such as excision with pyloroplasty or gastroenterostomy have been used in dealing with associated gastric and duodenal ulcers. However, in this

case, because of the extent of the lesions and the possibility of malignancy, gastric resection was done.

### SUMMARY

A case is reported in which gastric ulcer developed during a nine months period after the finding of a duodenal ulcer with retention. The possibility of the duodenal ulcer, with its resulting retention of gastric secretion, as a factor in the development of the gastric ulcer is discussed. The condition was relieved by extensive gastric resection.

### REFERENCES

1. Robertson, H. E., and Hargis, E. H.: Duodenal Ulcer: An Anatomic Study. *Medical Clinics of North America*, 8:1066-1092, January, 1925.
2. Walters, W.: The Choice of Surgical Procedures for Duodenal Ulcer. *Ann. Surg.*, 96:258-268, August, 1932.
3. Harper, F. R.: Development and Treatment of Peptic Ulcer: An Experimental Study. *Arch. Surg.*, 30:394-404, March, 1935.
4. Steinberg, M. E., and Starr, P. H.: The Factor of Spasm in the Etiology of Peptic Ulcers. *Arch. Surg.*, 29:895-906, December, 1934.
5. Elman, R., and Eckert, C. T.: Gastric Acidity as Influenced by Pyloric Closure and Stenosis. *Arch. Surg.*, 29:1001-1013, December, 1934.
6. Bolton, C.: Further Observations on the Pathology of Gastric Ulcer: Progress Report. *Proc. Roy. Soc. Med.*, 82:233, 1929.
7. Friedman, J. C., and Hamburger, W. W.: Experimental Chronic Gastric Ulcer. *J. A. M. A.*, 63:380, 1914.
8. Horsley, J. S.: Surgery of the Stomach and Duodenum. C. V. Mosby Co., St. Louis, 1933, pp. 60-61.
9. Puhl, H.: Die Anatomischen Grundlagen des Schmerzrezidivs nach Gastrojejunostomie wegen Magenduodenalgesehwurs. *Arch. f. Klin. Chir.*, 176:38-85, August, 1933.

## A NEW APPROACH TO DIETETIC THERAPY

By EUGENE FOLDES, M.D., New York City

Formerly Assistant Professor of Medicine, University of Budapest, Hungary

"This work teems with original thought . . . . It should be in the hands of everyone interested in dietetics and in dieto-therapy . . . . The chapter on the physiopathology of the stomach and upper intestinal tract is a classic."—*Med. Jour. & Rec.*  
 "The antiretentional treatment suggested is excellent. The discussion of organic types is unique. There will be an interesting and stimulating change in thought inspired in those who chose to investigate."—*Northw. Med.*  
 "This is a masterly book, off the beaten path . . . ." *Rev. Gastroenter.*

LEVER BOOK CO., AGENTS, 205 East 78th Street, NEW YORK CITY.

Price \$5.00

When combatting Pathogenic Organisms in the treatment of

## GASTROINTESTINAL TOXEMIA

ample germicidal and protozoacidal power combined with the lack of toxic action, point to the use of

### LIQUID ALPHA NAPHCO

and

### ENTERIC COATED CAPSULES

of

### JELLY of ALPHA NAPHCO

as a logical therapeutic agent of proved value.

The phenol coefficient, as against staphylococcus aureus in a medium of 50 percent blood serum and 50 percent saliva, in the case of the liquid is 3.1 and in the case of the Jelly, 6.2.

"Extensive laboratory work upon both animals and human subjects has thus far failed to establish any toxic limitation for these medications even though exceedingly large dosage has been employed."

For Laboratory Reports and Professional Samples, Address

CAREL LABORATORIES - Redondo Beach, California

# SECTION I—*Clinical Medicine: Diseases of Digestion*

## Recent Development in the Study of Oral Bacterial Flora\*

By

LLOYD ARNOLD, M.D.

and

CARROLL W. STUART, D.D.S., M.D.

CHICAGO, ILLINOIS

THE oral cavity has been considered by many to be normal in healthy individuals and to possess a rather constant bacterial flora. Those parts of the oral cavity of greatest interest to the dentist oftentimes are the first to undergo demonstrable secondary changes due to systemic or metabolic diseases. The oral cavity must possess some defensive mechanism against seeding itself with various and sundry types of bacteria. Several workers in this laboratory have studied the normal bacterial flora of the skin, nose, eye, gastro-intestinal tract and other body surfaces. We have included in our studies certain observations upon the mechanism of control of the endogenous and exogenous bacterial life on a healthy epithelial surface. This paper will record some of our work upon the bacterial flora of the oral cavity.

The first question to be discussed is the difficulty of finding a really healthy mouth. Allen (1913) said: "The artificial conditions of modern life have rendered it peculiarly difficult to secure for investigation an adequate number of individuals any part of whose respiratory tracts could be regarded as strictly healthy, especially from a bacteriological standpoint." There are persons whom we recognize as "carriers of pathogenic bacteria." For example, most people harbor the *Mierococcus catarrhalis* in their nasal passages and yet rarely suffer from the acute reaction, others carry pathogenic strains of pneumococcus or perhaps strains of *Bacillus diphtheria* may be cultured from human throats without the person ever suffering with these diseases. They may even be entirely ignorant of harboring such organisms. We might try to conclude that these bacteria are not pathogenic if we were not sure the contrary to be the case. A very thorough examination of every mouth and throat will disclose various sized areas of gingivitis, a carious tooth, paradental gingival pockets perhaps around the third molar, follicular tonsillitis, inflamed dental papillae, an infection in the supratonsillar fossa which is always difficult to detect, a granular pharyngitis, or some other condition of which the patient may not be aware. Any one of these infected areas will so change the oral flora

that we have no right to classify the mouth as a normal. A review of the literature leads one to conclude that with one or more of these conditions classed as a normal then the numbers, types, and strains of bacteria to be found are so varied as to render the problem of investigating a normal mouth a hopeless task. Allen (1913) therefore, stated: "Any attempt at discussion as to what is the bacteriology of the healthy mouth would be of purely academic interest, inasmuch as the perfectly healthy mouth is for all intents and purposes non-existent."

Our investigations not only bore out the findings of Allen and others but led us to conclude that even the different areas of the mouth vary in bacteriological content. Changes in the bacterial flora were noted on the same areas in a relatively short time. This was especially characteristic on the dorsum of the tongue.

It is reasonable to expect to find a great variety of micro-organisms in the oral cavity because the air we breathe, the water we drink, and the food we eat contain innumerable species of bacteria. The lips come in contact with many different articles during a day, thus frequently seeding bacteria onto the mucosa of the lips. The tongue licks the bacteria back into the oral cavity from this seeding zone in great numbers. Food may be deposited in crevices of the tongue and the gums, in cavities of the teeth, and the interdental spaces between the teeth where the bacteria in such particles may grow under ideal environmental conditions. Miller (1892) described over 100 different varieties of micro-organisms in the mouth and the more carefully we go into this problem with modern methods the greater are the varieties which come to light until we are entirely bewildered and confused in an almost mass of bacterial species.

J. and R. Cruickshank (1931) stated that the bacterial flora of the mouth is extremely complicated and in addition may undergo variations from time to time and these factors place a great variety of difficulties in the way of investigating pathological lesions of the gums and teeth. The authors state that the view so widely held by clinicians, that many general bacterial infections and toxemias in the human subject have their portal of entry in carious or dead teeth and are disseminated by the associated lymphatics, rests upon

\*Department of Bacteriology and Public Health, University of Illinois, College of Medicine, and Research Laboratories of the State Department of Public Health, Chicago, Illinois.

Read before the Chicago Dental Society, February 19, 1935.  
Submitted April 28, 1935.

slender bacteriological foundations. The factors just mentioned render research on this aspect of medicine a subject of great complexity. These writers found that the bacterial flora of the mouth changes from week to week and even from day to day. They conclude that the types of research carried out recently by groups of observers who take swabs from the throats of many individuals at monthly intervals and tabulate the percentage of persons harboring certain organisms is of little value.

The adventitious or exogenous bacterial flora of the mouth is that which is constantly gaining entrance with air, dust, food, and water. It is this flora that is constantly being eliminated and seems to be very transient. Miller (1890) was one of the first to point out how rapidly the adventitious flora was removed from the mouth. He rinsed his mouth with highly concentrated suspensions of lactic acid bacilli and was able to show practically none of these organisms present by the next morning. Bloomfield (1919, 1920, 1921) called attention to the rapid disappearance of foreign organisms by the flushing mechanism of the mouth secretions. He expressed the opinion that except for local infections or transient invasion under special conditions, transient organisms do not as a rule grow freely on the mucous membrane of the oral cavity. In his review of the literature concerning the protective mechanism of the mouth he lists the possible factors of importance as: (a) anatomical conditions, (b) the flushing mechanism, (c) bactericidal action of secretions, (d) reactions of the secretions, (e) the antagonistic action toward invaders of the endogenous flora.

Bloomfield (1922) referred to the circulation of bacteria in the mouth. He described how bacteria, by means of suction currents, were carried from the lips backward toward the throat. These transient organisms are not easily attached to the mucous membrane of the mouth but once they do become fixed to the tissues it is very difficult to dislodge them. This investigator attempted to remove the bacteria from the dorsum of the tongue by frequent washing, scrubbing, and irrigations which were carried out at 20 minute intervals. He was able to dispose of the transient bacteria but none of the attached flora. It is evident, therefore, that the bacteria of the normal flora do not grow freely in the mouth secretions but may do so in the crevices of the mucous membranes and in the openings of the ducts of the glands. The organisms which had become attached to the mucosa could not be dislodged by the application of an hypertonic salt pack. He concludes that any of the organisms which remain in the mouth for a few hours must be in "vital biological relationship" to the mucous membrane, or they would be removed by mechanical means. Furthermore, the saliva plays no significant role in the propagation of bacteria but can assist as a vehicle in the process of expectoration and swallowing which after all are the two most important methods of bacterial elimination from the oral cavity and throat.

The intrinsic or endogenous flora consists of those organisms which are attached to the tissues and, according to Edington (1922) are introduced with food, water, and air, but Thomson and Thomson (1932) were unable to obtain cultures of bacteria which make up this flora from food, water, and air. They con-

clude that these bacteria are derived from previous human beings and perhaps animals.

Attention has been called to the fact that the oral flora varies in the different anatomical parts of the mouth and throat. Brailovisky—Lounkevitch (1915) found, upon examination of the cheeks, tongue and palate, organisms which were comparable with the flora of a suckling child, together with a different bacterial flora from the tongue and gums. Small and large gram-positive diplococci predominate in the films taken from these areas and with them were found a few leptothrix and spirilla. The same diplococci are found in great numbers on the tongue in addition to masses of staphylococci, short and long thin rods, spirochetes, leptothrix, filaments, and vibrios. The gums harbored a few cocci and other organisms occurred in numbers in different individuals; in some mouths great numbers of slender gram negative rods predominate, in others filaments of leptothrix and still in others spirochetes. Bacteria occurred in greater abundance among the villi on the back of the tongue than on the tip. The numbers vary greatly between the teeth, but the types consisted almost constantly of leptothrix threads, spirochetes and fusiform bacilli. The habitual flora of the mouth of adults was about the same as that of the child after dentition but greater variations occur according to the state of the mouth and the teeth. The fundamental flora consisted of streptococcus salivarius, together with various anaerobes, leptothrix, spirilla, vibrios, staphylococci and others.

The condition, as well as the arrangement of the teeth (presence of caries apparently affects the picture) and careful hygiene all materially influence the numbers of bacteria making up the flora. Complete removal of all of the teeth is associated with a return of the types of organisms to those found in the mouths of suckling infants. Space will not permit of a complete description of all anatomical areas.

There does not seem to have been much work done on the effect of the diet on the bacterial flora of the mouth. Howitt, Fleming, and Simonton (1928) placed a patient on each of several diets for a week at a time: (1) the usual diet, (2) two types supposed to have a detergent effect, (3) balanced diet, and (4) a so-called "sticky" type of food. Each diet was given at least twice, once with the use of the tooth brush and once without. In addition the patient was given liquid food through a stomach tube, and no tooth brush was used. Weekly quantitative and qualitative examinations were made of the mouth flora. Mouth organisms flourished readily on desquamated epithelium in the absence of food particles. The debris gathered after a sticky diet showed no more abundant growth than that after supposedly detergent diets except for a slight increase of aciduric rods on carbohydrate diet. Artificial cleansing with the tooth brush was more effective than a detergent diet, and when the tooth brush was not used the teeth were cleaner following the "sticky", balanced and ordinary diets than on detergent diet. When the tooth brush was used the appearance was similar in each case. One of their workers was used as a subject for a study of throat cultures over a period of a year. During this time he developed a duodenal ulcer and was fed through a tube passed into the duodenum. All food and water was administered via this tube. Throat cultures taken, during the time when no food or water touched the throat mucosa,

were similar to the findings obtained when he was on a normal diet.

Kuster (1913) states that nothing was known as to whether or not the normal bacteria in the mouth play any useful role in digestion or in keeping the mouth clean. During health the bacteria are evidently harmless but during times of lowered resistance and when the patient is suffering with local and systemic diseases these same organisms may penetrate into the deeper tissues and cause considerable damage. Kuster believed this occurs in cases of pyorrhea, diseases of the teeth and jaws, in necrotic anginas and in cancrum oris. When the organisms were swallowed and came in contact with the acid of the stomach they were dissociated or changed to a non-pathogenic state and never, under normal conditions, reach the duodenum unchanged. This was the reason why these organisms are considered to be absent in the duodenal flora. The bacteria found in the intestines are entirely different than those found in the oral cavity.

Thomson and Thomson (1932) state: "It seems to us that the bacteria of the mouth are of no value in human economy, except that perhaps their presence on the mucous membrane may prevent the settling down of other more dangerous bacteria. They may also stimulate the production of antibodies." . . . "It is our opinion our health would be greatly benefitted if the mouth could be kept sterile." Obviously good hygienic conditions of the oral cavity is of great value to health. Thomsons' definition of oral hygiene consists of the scrupulous cleansing of the teeth and gums, and the removal of all dead organic matter and debris. They recommend cleansing the mouth by the frequent use of the tooth brush and by the use of the weakest of antiseptic solutions. They contend that cleansing the oral cavity by washing was brought about more by the mechanical removal of bacteria and debris than by antiseptic action. The local production of acid has been thought to prevent putrefaction and fermentation but on the other hand weak acid solutions in contact with the teeth has been related to dental caries. The results of these findings and their value to health remain to be established.

The physiology and biochemistry of the oral secretions should be considered as their possible influence upon the bacterial flora of the mouth. The mucous membranes of the cheeks, palate, gums and tongue are covered with squamous epithelium and there are no cilia such as are present in the nose and nasopharynx. On the tongue there are microscopic papillae like those of the skin. Besides these the upper surface of the tongue is covered with larger papillae of three kinds: (1) the circumvallate papillae at the back of the tongue, (2) the conical papillae which are scattered over the entire surface, and (3) the fungiform papillae which are found among the conical papillae.

Mucus is secreted through most of these papillae but the glands of Ebner which open between the circumvallate papillae and a few others elsewhere in the mucosa secrete a serous material. In addition to these mucous and serous secretions the saliva flows in large amounts from the parotid and sublingual glands. Great numbers of epithelial cells are shed from the mucous membrane. The mucin and dead epithelial cells serve as an excellent culture media for bacteria which are

found on the surface in large numbers. Goodby (1931) concludes that the shedding of the epithelial cells is another way of cleansing the mouth. A film made from the buccal mucous membrane and stained with Leishman's stain shows a number of epithelial cells which have become detached and which are surrounded by large numbers of bacteria. Goodby believes the most important method of cleansing the oral cavity is the stirring up of the oral secretions by the mechanical movements of the cheeks and tongue.

About 90 years ago Eberle reported a personal experience in which saliva had toxic effects and was dependent upon emotional conditions. As a matter of fact, this theory was probably first suggested by Galen. Several workers, including Pasteur (1881), isolated many pathogenic organisms from the saliva. Many workers have described a number of strains of bacteria which were not pathogenic but were found to grow in oral secretions. Thomson and Thomson (1932) conclude, however, that: "There can hardly be any doubt that any poisonous effect of the saliva is likely to be due to its bacterial content rather than any chemical toxic substance present in it."

We know that the secretions of the glands of the mouth are under the control of "sympathetic and cranial nerves," and that nervous and psychic reactions materially influence these secretions. Kuster (1913) states that the secretions of the salivary glands in healthy persons has either a neutral or weakly alkaline reaction but it does become weakly acid in some of the constitutional disturbances. He also states that various reactions may be obtained from different parts of the mouth. For example, under certain conditions the moist tongue may be weakly alkaline while the interdental spaces and crypts of the mucous membrane are acid. Bloomfield and Huck (1920) carried out some hydrogen-ion concentration measurements and found that freshly expectorated saliva from normal persons gave a reaction varying from pH 6.0 to 7.5 with 80% of the specimens falling between pH 6.6 and 7.1. The reaction varied in the same individual at different times without any relation to the time of the day or the digestion of food or fluids. The use of mouth washes such as Dobell's solution caused a change in reaction of the saliva for about 30 minutes only and the internal administration of acids and alkalis did not alter the reaction in the least. There is no definite change in the hydrogen-ion concentration of the saliva in patients suffering from certain diseases. Marshall (1924) found the reaction of the saliva followed the buffer contents of the blood.

Florain and Sanarelli (1913) carried out experiments on filtered germ free human saliva and found it not only a poor culture medium but slightly inhibitory to bacterial growth. Kuster explained the story so frequently told about the dog that licks its wounded foot. It is thought that the saliva possesses some antiseptic value and for that reason the wound on the dog's foot heals rapidly when it is licked. He states that many of the dogs die from such wounds even though they are bathed in saliva frequently during the process of licking. On the other hand, when a dog licks a wound he not only mechanically cleanses it but also promotes free drainage and produces marked counter-irritation which aids the healing process even though the saliva has not antiseptic value. We may,

therefore, conclude that saliva has not been proven to possess chemical antiseptic properties.

### AUTHORS' STUDIES

Experiments were carried out in our laboratory by Arnold, Ostrum, and Singer (1928) concerning the auto-sterilizing power of the mucous membrane of the nose. Bacteria placed upon the normal mucous membrane of the nose, for some reason, disappear within a relatively short time. Since that time the investigation has been carried out over most of the exposed surfaces of the body and we find a very complete protective mechanism in the form of a self-sterilizing power of the skin and some of the mucous membranes of the body. This same type of investigation was carried on within the oral cavity and we obtained some very interesting results.

Miller and Ryan (1932) working in our department on the economical and practical methods of sterilizing clinical thermometers for hospital practice, found that after the thermometer had been removed from the mouth and rolled over the surface of an agar plate, there was a narrow band of small white colonies 2-3 mm. wide extending along the path of the thermometer. This zone was close to the protruding free end of the thermometer. Further investigation showed this band to correspond to the place where the lips were in contact with the glass. In many instances the only growth of bacteria was limited to this narrow area which was identified by an almost continuous band of colonies. These observations led us to make a more thorough study of the lip regions.

Our preliminary studies soon indicated that definite anatomical areas had to be chosen and individual observations made of each region. We, therefore, divided the mucous surface of the mouth into (Fig. 1):

Region 1. The skin surface immediately below the junction of the skin and mucous membrane of the lower lip.

Region 2. The junction of the skin and the mucous membrane of the lower lip.

Region 3. The moist zone of the lower lip which meets the upper lip.

Region 4. The midline of the lips.

Region 5. The junction of the mucous membrane and the skin of the upper lip.

Region 6. The moist zone of the upper lip which meets the lower lip.

Region 7. The corners of the mouth.

Region 8. The vestibule of the mouth.

Region 9. The labial surface of the lower gums.

Region 10. The lingual surface of the lower gums.

Region 11. The frenulum of the tongue.

Region 12. The tip of the tongue.

Region 13. The midline of the tongue.

Region 14. The side of the tongue.

Region 15. The dorsum of the tongue.

Region 16. The base of the tongue.

Region 17. The mucous surface of the cheek.

Region 18. The anterior pillar.

Region 19. The hard palate.

We first studied the endogenous flora of these areas by moistening sterile cotton swabs in normal saline solution which were brushed over the mucous membranes and then seeded upon plain agar plates. Our first purpose was to learn the relative density of the bacterial population residing on the surfaces of the areas under investigation. We performed about 100 such experiments; the averages from this number of

seedings are given as the final result obtained. Several hundred cultures were made.

The areas of the lips showed smaller colonies than those taken from elsewhere in the mouth. The order of predominance were: *Staphylococcus aureus*, *Staphylococcus citreus*, and *Staphylococcus albus*. Blood agar plates showed *staphylococcus* and *Streptococcus hemolyticus* occurred at the corners of the mouth, on the midline of the lips, and the tip of the tongue. The heaviest growths were obtained from the narrow zone of contact of the upper and lower lips, the side, dorsum, and base of the tongue, the surface of the cheeks, the anterior pillar, and the palate. The relative density of bacterial flora was found as follows: the midline of the tongue, tip of the tongue, lingual surface of the lower gums, corners of the mouth, midline of the lips, moist zone of the lower lip which meets the upper lip, the vestibule of the mouth, the labial surface of the lower gums, but the junction of the mucous membrane of the lower lip and the skin was almost sterile and we found no growth at all over the frenulum of the tongue.

Our next investigation was directed toward studying the auto-sterilizing power of the mucous membranes of the mouth and also the highways which are used by the transient bacteria. The same technique was carried out in this problem as was used in studying the auto-sterilizing power of the skin. This consisted of washing off the *Bacillus prodigiosus* growth on a

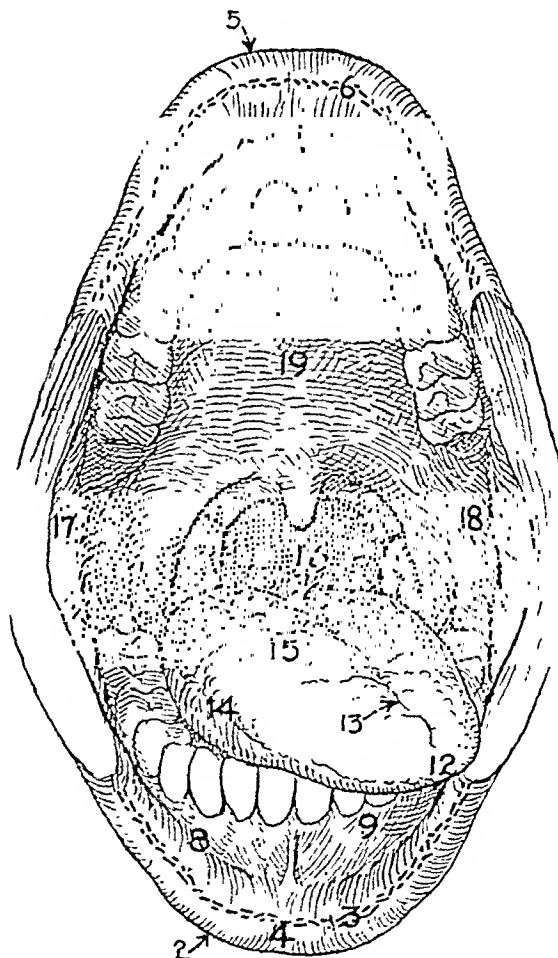


Fig. 1



plain agar plate with 10 cc. of saline, and diluting this with normal saline solution 1 to 100,000. A sterile cotton swab was saturated in this solution and a plain agar plate was seeded from this swab as a control. To avoid the mechanical removal by oral secretions a double saliva ejector was held in the mouth while a saturated sterile cotton swab, as above, was used to seed *Bacillus prodigiosus* organisms upon the area under investigation. Other sterile cotton swabs were brushed over different but adjoining areas on the region at five minute intervals and plates were inoculated with these swabs. We frequently waited two or three days before reading the plates to allow the full pigmentation of colonies to develop.

The first area to be studied was the labial surface of the lower gums near the gingivus. The results obtained over a period of 40 minutes showed practically no disappearance of the *Bacillus prodigiosus* organisms from this area. That is to say that here is an area where there is little or no auto-sterilizing power of the mucous membrane. Bacteria seeded upon this area may remain unchanged, except for mechanical removal, for a relatively long time and if these were pathogenic bacteria they would still be able to produce diseases. The experiment was repeated and the mouth was allowed to assume as normal movements as possible but our findings were so varied that we are unable to give a definite group of figures. This does tend to show, however, that the mechanical movements of the mouth markedly influence the removal of bacteria.

The next area investigated was the side of the tongue with the same technic and the use of the double saliva ejector. On this area we found a marked decrease in the number of bacteria grown on the plates which were seeded from the region over a period of 40 minutes. With 313 colonies on our control we found at the end of the first five minutes 246 colonies and only 56 colonies at the end of 40 minutes. We may conclude that the side of the tongue is capable of destroying bacteria without the aid of any washes, antiseptics, or brushes.

The usual technic was again used in studying the mucous membrane of the cheek. The control showed 414 colonies. At the end of five minutes the plates gave a reading of 138 colonies and at the end of the 40 minutes only 9 colonies were grown. It is evident that the cheek too may sterilize itself. These figures were so striking that we considered the flow of secretions of the parotid gland down the cheek as a possible source of error. We, therefore, placed a canula in Stenson's duct in order to completely control the flow of saliva. Upon repeating the experiment under these conditions we obtained results which substantiate those of the previous experiment and again proved the self-sterilizing power of the mucous membrane of the cheek.

We then turned our attention to the pathways over which the transient bacteria travel as they pass backward from the lips over the dorsum of the tongue to the throat. We divided each lateral half of the dorsum of the tongue into three equal longitudinal parts. A suspension of *Bacillus prodigiosus* was swabbed upon each area and plates were seeded from these zones by swabs taken at five minute intervals. The double saliva ejector was used and the tongue was held in a fixed position. The results were much the same as those obtained from the gingival margin which showed relatively little if any disappearance of bacteria.

A suspension was then swabbed on the lips and the normal movements of the mouth were permitted as nearly as possible. The lips were licked in the usual manner and swabs taken not only from each of the three zones but from adjoining fields at three minute intervals and each specimen was seeded on a plain agar plate. The results were not so constant as we should have liked but an analysis of the colony count proved that the highways by which bacteria travel toward the throat is approximately the middle third of each lateral half of the dorsum of the tongue. The tip of the tongue was surprisingly free from test bacteria but there was an area on the margin about  $1\frac{1}{2}$  cm. lateral to the midline over which the bacteria passed in the beginning of their travel backward. The speed with which the organisms move seems to be in relation to the firmness with which the tongue is pressed against the palate and the amount of suction produced. The average movements of the bacteria in a backward direction is very rapid. At times *Bacillus prodigiosus* were found at the base of the tongue in the first three minute interval after licking the lips.

### DISCUSSION

When we consider the bacterial flora of the oral cavity we must think of two distinct groups of organisms: the intrinsic or endogenous, and the transient or exogenous flora. The intrinsic flora is made up of these organisms which have become attached to the cells, are between the papillae, in the crypts and may be found in the openings of the ducts of the glands. These organisms do not produce disease and may be considered as the normal flora. Their purpose is not definitely known but they persist regardless of the most radical methods used to remove them.

The transient or exogenous group of bacteria are those organisms which are introduced into the mouth not only by the air, food, and water, but also by the licking of the lips which have become contaminated from eating utensils, public drinking cups or fountains, etc. These transient bacteria travel backward toward the throat at a rapid rate which is in proportion to the amount of suction produced when the tongue is pressed firmly against the palate. In some cases only two or three minutes is required for an organism to pass from the lips to the base of the tongue and throat. These are the bacteria which are foreign to the individual and if no resistance has been developed against them they are the organisms which are capable under certain conditions of producing disease. We were unable to find evidences of bacteria passing from the throat into the mouth.

The mechanical removal of bacteria and the auto-sterilizing mechanism of the mucous membrane of the oral cavity are the most important factors in the elimination of bacteria from the mouth. The saliva is neither a good culture medium for bacteria nor does it possess antiseptic properties. As the saliva is stirred up by the movements of the tongue and cheeks it materially assists in the mechanical removal of bacteria from the many fields within the oral cavity. The hydrogen-ion concentration of the saliva is in direct proportion to the buffer content of the blood, as well as the carbon dioxide tension of the expired air, and although it does vary within wide limits under normal conditions there is nothing which may be used locally or by internal medication that will change the reaction for more than a few minutes at a time.

Diet has little if any influence upon the reaction of the saliva or upon the bacterial flora of the mouth. Oral hygienic procedures consist primarily of cleansing the mouth of food debris and brushing foreign materials from the surfaces of the teeth, but antiseptic mouth washes are of little value except as a mechanical factor in the removal of bacteria, the same as sterile water.

The self-sterilizing power of the mucous membrane of the mouth is one of our most important protective mechanisms against bacterial invasion by the transient group of organisms. The highways over which these transient organisms pass is rather limited to the middle longitudinal third of the dorsum of the tongue. The cheeks, side and frenulum of the tongue maintain a very perfect auto-sterilizing mechanism but the surface of the gums near the gingival margin,

the dorsum of the tongue, and the palate show little ability to destroy bacteria.

The lips are apparently a primary seeding zone for the mouth. The narrow zone of contact of the lips is an area which, when inoculated with organisms, seems to furnish an unlimited supply for almost continuous contamination of the oral cavity. It is evident that chronic infections of the mouth call for a close inspection and examination of not only the gums, interdental spaces and dorsum of the tongue but also the mucosa of the lips.

The investigations of the bacterial flora of the mouth have made little progress over a long period of time but now that we are beginning to understand the normal physiological processes which are going on in the oral cavity we expect the problems will unfold themselves in the future.

## REFERENCES

- Allen, R. W. (1913): Bacterial Diseases of Respiration and Venecies in Their Treatment. Lewis, London.
- Araold, L.; Ostrum, M., and Singer, C. (1928): Auto-sterilizing Power of the Nasal Mucosa. *Proc. Soc. Exp. Biol. and Med.*, 25:624.
- Bloomfield, A. L. (1919): The Fate of Bacteria Introduced into the Upper Air Passages. *Amer. Rev. Tuberc.*, 3:553.
- Bloomfield, A. L. (1920): The Fate of Bacteria Introduced into the Upper Air Passages. II. *B. coli* and *Staphylococcus albus*. *Bull. Johns Hopkins Hosp.*, 31:14-55.
- Bloomfield, A. L. (1920): The Fate of Bacteria Introduced into the Upper Air Passages. V. Friedlander Bacilli. *Ibid.*, 31:203-206.
- Bloomfield, A. L. (1920): The Upper Air Passages as an Environment for Bacterial Growth. *Amer. Rev. Tuberc.*, 4:247.
- Bloomfield, A. L. (1921): The Significance of the Bacteria Found in the Throats of Healthy People. *Bull. Johns Hopkins Hosp.*, 32:33.
- Bloomfield, A. L. (1921): The Localization of Bacteria in the Upper Air Passages: Its Bearing on Infection. *Ibid.*, 32:290.
- Bloomfield, A. L. (1922): The Dissemination of Bacteria in the Upper Air Passages. II. The Circulation of Bacteria in the Mouth. *Bull. Johns Hopkins Hosp.*, 33:145-149.
- Bloomfield, A. L., and Huck, J. G. (1920): The Fate of Bacteria Introduced into the Upper Air Passages. IV. The Reaction of the Saliva. *Bull. Johns Hopkins Hosp.*, 31:118.
- Brnilovsky-Lounkevitch, Z. A. (1915): The Normal Flora of the Mouth. (Contribution à l'étude de la flore microbienne habituelle de la bouche normal: Nouveaux-nés enfants, adultes). *Ann. de l'Institut Pasteur*, 29:379.
- Cruikshank, J., and Cruikshank, R. (1931): The Common Cold. *Annals of the Pickett-Thomson Laboratory*, 8:58.
- Edington, D. C. (1922): Streptococcal Infection by the Nasal and Buccal Paths. *Brit. Med. Jour.*, Feb. 25th, pp. 304-306.
- Florain and Sanarelli (quoted by Kuster (1913). No reference given. The Common Cold. *Annals of the Pickett-Thomson Laboratory*, Vol. 8, (1932).
- Goadby, K. W. (1931): Diseases of the Gums and Oral Mucous Membrane. *Oxford University Press*, Milford, Oxford, pp. viii. + 496.
- Howitt, B. F.; Fleming, W. C., and Simonton, F. V. (1928): A Study of the Effects upon the Hygiene and Microbiology of the Mouth of Various Diets, without and with the Use of the Toothbrush. *Dental Cosmos*, 70:575.
- Kuester, E. (1913): Die Flora der normalen Mundhöhle. *Kolle u. Wassermanna*, Vol. 6, 2nd Edition, pp. 435-449.
- Marshall, J. A. (1924): Physiological Review, 4:564.
- Miller, W. D. (1890): Microorganisms of the Human Mouth. 9:72.
- Miller, W. B. (1892): Die Mikroorganismen der Mundhöhle, Leipzig.
- Miller, V., and Ryan, V. (1932): Disinfection of Clinical Thermometers. *Amer. J. Nursing*, 32:197.
- Pastour, L. (1581): Note sur une Mladie nouvelle provoquée par la salive. *Bull. de l'Acad. de Med.*
- Thomson, D., and Thomson, R. (1932): The Common Cold. *Annals of the Pickett-Thomson Laboratory*, 8:57.

## Gastroscopy: Past, Present and Future

By

EDWIN BOROS, M.D.\*  
NEW YORK CITY, NEW YORK

SINCE the origin of the concept of the direct inspection of the stomach through the use of an orally introduced instrument by Kussmaul, there have arisen workers, from time to time, whose labors and enthusiasm in this field have furthered such a procedure, as an advancement in the diagnosis of diseases of the stomach. Amongst these pioneers in this new approach, there may be mentioned Nitze, Mikulicz, Rosenheim, Kelling, Loening and Stieda, Sussman, Elsner, Schindler and Jackson, in this country.

During this era of development, suggestions for various methods of exploration in this fashion, supplemented by the addition of newer and improved instruments which were more likely to facilitate and establish this method as a safe and reliable procedure, were undertaken and practised. Despite disappoint-

ments and obstacles, the enthusiasts in this work clung to the hope and expectation that the innermost recesses of this wholly unexplored viscus would be amenable to exploration, and result in the establishment of an acceptable aid to our diagnostic and therapeutic armamentarium.

It might be mentioned, that, not without warranted distrust and condemnation, efforts in this direction were subjected to considerable criticism, for the instruments consisted of rigid tubes for the most part, of a character which did not require much exertion to do damage and to endanger the patient; frequently the results were alarming. Furthermore, the ordeal of the introduction, the oft adverse reaction of the patient, all this did not serve particularly to enhance the general acceptance of gastroscopy as a routine procedure of examination. It might be emphasized, that the re-

\*Associate Gastroenterologist to the Bronx Hospital.  
Submitted April 16, 1935.

sults of the examinations already conducted, bearing in mind the limited visibility of a considerable portion of the gastric mucosa to the examining eye, served to occasion doubt and distrust not only as to the actual value of the procedure but to its practicability as well.

Nevertheless, it is phenomenal, and one cannot help but marvel at the enormous skill and dexterity with which this seemingly dangerous introduction of the rigid tube into the stomach, was and is still being practised without ill effects to the patient. Recognition soon gained ground, that if the arguments of the opposition were to be met, that a way must be found which would allay the fears already noted. Accordingly, a flexible apparatus was evolved, in the expectation that this type of gastroscope would eliminate the dangers experienced with the introduction of the rigid tubes. This type of instrument was however, not without fault. It remained for Rudolf Schindler to develop the present model, which is a combination of a semi-flexible and rigid tube, encasing a lens system for observation. The angle of vision of this new instrument is 60 degrees, and enables the examiner to explore the greater portion of the stomach, inclusive of the pylorus and cardia. The length of this gastroscope is 68 cm. without its rubber attachment.

At the present time, we are using the Wolf-Schindler gastroscope. We are convinced that the objections of the many antagonists to the rigid tube gastroscopy have been overcome. Needless to state, there are definite contraindications to the introduction of the Schindler improved apparatus, which cautions must be fully and at all times observed if one is to avoid accidents to the patient. Further, one must not expect this method of examination to displace those means which we already have at our disposal for the evaluation of the many problems present in the diagnosis of gastric disease. Gastroscopy is meant to *supplement*, not *supplant* the usual physical, chemical and roentgenological examinations of the patient.

It is to be remembered, that in gastroscopy, the *positive* findings are of importance. A negative examination by no means precludes the possibility of an undetermined lesion, any more than occurs in the course of a roentgenologic examination of a patient, and of course, this element is to be appraised in the light of the skill and experience of the gastroscopist, as well as in the recognition that all areas of the gastric mucosa are not discernible. It might be well to mention here, that in order to limit the unexplorable areas of vision of the gastric mucosa, it is advisable to have recourse to both types of gastroscope, the straight and the curved tipped instruments. The proper selection of either of these instruments will tend to reduce errors to a minimum.

In contrast to the open tube, the Wolf-Schindler system confines the examiner to the inspection of the interior of the stomach. Whereas an opportunity is afforded to *study* lesions and diseases in various stages of development and progress, to note properties and characteristics of different processes, degrees of healing and advance or retrogression in the course of a gastric affection, yet the removal of tissues for microscopic examination, instrumentation or possible topical applications for therapeutic purposes is possible only by means of the open tube. Observation through the closed tube gastroscope permits at the present time study and recognition of the early manifestations of local or systemic diseases, helps to differentiate lesions of a doubtful nature by actual visualization, enables one to note changes in form and function in a manner hitherto impossible and permits observations as to the course and duration of disease as well as the effects of therapeutics.

As for the possibilities: it needs but little emphasis to remind one of the vast prospects, not only in the evaluation of those conditions already known to us, but also in a field where knowledge may be enriched and new vistas and promises of greater satisfaction afforded as new revelations unfold themselves.

---

## A New Tube For Anaesthetization of the Hypopharynx

By

RUDOLF SCHINDLER, M.D.\*  
CHICAGO, ILLINOIS

---

IT is customary to anaesthetize the throat before executing an esophagoscopy or a gastroscopy. There are some authors who have not found it necessary. It certainly renders the procedure less disagreeable, and in my experience has been found to be of distinct advantage.

In anaesthetizing the hypopharynx, it is necessary to introduce an anaesthetic on an applicator beyond the *musculus constrictor pharyngis*. This procedure can be extremely difficult in some patients, due apparently to spasm of the constrictor muscles of the pharynx. Some patients contract their muscles convulsively when a hard metal applicator is introduced into

the pharynx, whereas a simple rubber tube can usually be passed without difficulty. Much patience and ingenuity are often necessary at this stage. Therefore the author has always emphasized that this can be the most difficult part of the entire endoscopic examination. On one occasion in his experience an accident occurred in which, as a result of the resistance of the patient, the cotton became separated from the applicator, allowing its sharp point to inflict trauma in the upper esophagus, which was followed by an abscess.

Therefore it seemed necessary to devise a different method for anaesthetizing the hypopharynx. The fact that even the most resistant patient swallows the soft rubber tube easily suggested the possibility of using

\*Visiting Professor of Medicine, University of Chicago, Chicago, Illinois.  
Submitted May 14, 1935.

such a tube with holes cut in the walls. This was not entirely satisfactory, for when the anaesthetic liquid was injected through such a tube, it flowed out through the upper holes only and the desired effect was not ob-

withdrawn. The type of local anaesthetic used is important. Cocaine should not be chosen because it is toxic. Most of the other substitutes do not have an adequate anaesthetizing effect. Moutier, however, ad-

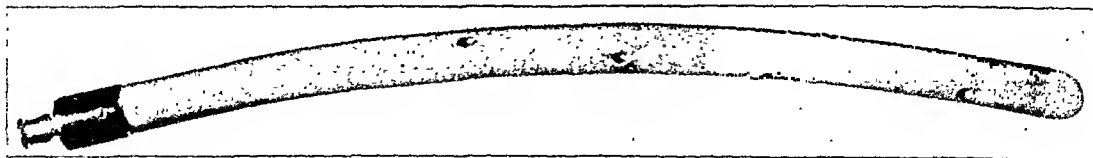


Fig. 1. Photograph of Anaesthetization Tube.

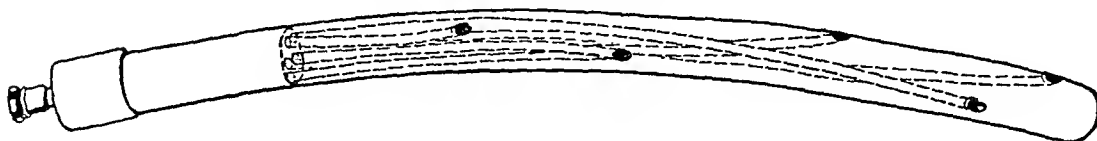


Fig. 2. Diagram illustrating construction of anaesthetization tube.

tained. A better result was secured by filling the tube with cotton.

This led to the construction of a rubber tube containing a number of smaller tubes, each opening through the walls of the outer tube. The upper end of the large tube carries a metal connection for the insertion of the syringe. (Figs. 1 and 2).

By this construction the anaesthetization of the hypopharynx is now greatly facilitated. The patient swallows the tube, the anaesthetic fluid is injected with a syringe through the tube, and the tube is then

withdrawn. The type of local anaesthetic used is important. Cocaine should not be chosen because it is toxic. Most of the other substitutes do not have an adequate anaesthetizing effect. Moutier, however, ad-

vises the use of a 10% solution of "Delcaine". I have found a 2% solution of "Pantocaine" very satisfactory. Five cubic centimeters of this 2% solution are injected through the tube as described. It is advisable to repeat the procedure after five minutes. Then the mucosa is insensitive.

As a result of this procedure the danger of trauma in the anaesthetization of the pharynx has been eliminated. This renders the entire endoscopic examination much less uncomfortable, and considerably shortens its duration.

## ABSTRACTS

YEGGE, W. BERNARD.

*A Critical Review and Evaluation of Tests for Liver Function. Ann. Int. Med., VIII, 907, February, 1935.*

The author prefaces his article with some reminders of physiological fundamentals, such as the functions of the liver and a statement that a large amount of structural change may obtain before functional disorders are in evidence, and its contrary corollary, that a marked alteration in function may obtain without any structural change. He follows a plan adopted by most of the recent authors in considering the various tests under headings of liver function, but cautions that while many tests for separate functions of the liver have been devised, none has been advanced that will evaluate these functions as a whole, hence it is necessary to study these functions separately.

*Cholecystography* is looked upon as a method of differentiation between gall bladder and liver disease, rather than having a bearing as a test for liver function. Of *transduodenal drainage* procedure he says that the microscopic study of bile obtained by duodenal drainage is important, as it may reveal evidence of definite infection or of crystals of cholesterol or calcium butyrate, which are important in the diagnosis of cholecystic disease. He stresses the importance of an estimation of the *bilirubin* and thinks of the *icterus index* as the simplest method. He calls attention to its importance in subclinical jaundice, but cautions that in chronic liver disease it is of

little value except to follow the course of the disease and to detect the early onset of jaundice. In referring to the *van den Bergh test*, attention is called to the recent findings of Jacobi, which indicate that the plasma and the serum may be used with equal accuracy in the determination of bilirubin. Special emphasis is laid on the so-called diphasic reaction of the van den Bergh, which may be found in toxic or infectious jaundice, and in hemolytic jaundice, when the increased viscosity of the bile may result in blockage of bile capillaries in both forms of bilirubin in the blood. Laboratory data covering a *destruction of red blood cells* is not considered a test of liver function, but rather one of hemolytic jaundice, since this function is shared by other organs of the body through the reticulo-endothelial system. He thinks the determination of the *coagulation time* of the blood is a very important test of function of the liver, since when the liver is damaged to any extent, the blood fibrinogen is increased and the clotting time of the blood is increased. The *sedimentation test* is considered very useful in conjunction with the coagulation test in order to detect the hemorrhagic tendency. Some attention is given to a test for determination of *fat metabolism*, and Whipple's method is advised, but he concludes this phase of the subject by stating that he has not had enough experience with estimations of blood lipase to give an opinion as to its value. The *hemoclastic crisis test* has very little value, he thinks, in the diagnosis

of liver disease, since other factors beside liver damage cause a variation in the leucocyte count and the other phenomena. Conceding the determinations of uric acid as a valuable means of studying liver function in dogs, he thinks that it has not been proven of value in humans, due to the fact that large injections of uric acid may cause lesions in the kidneys. Of a determination of guanadin in the blood, he says that while it is increased in patients with acute arsphenamine hepatitis, acute catarrhal jaundice and predisposition to toxemia and eclampsia, there is no deviation from the normal blood guanadin in chronic liver diseases such as carcinoma, syphilitic hepatitis, alcoholic cirrhosis and obstructive jaundice. In determining impairment of liver function in the role of carbohydrate metabolism, he favors the *galactose test*. Elimination of any amount over 3 grams of galactose in five hours is considered as an evidence of hepatic impairment. Attention is invited to the fact that in obstructive jaundice without liver damage and in hemolytic jaundice the readings are normal.

No definite conclusions are expressed from the Author's experience with tests to determine the antitoxic and protective functions of the liver, but speaks hopefully of the possibilities for future study. The *Bromsulphthalein* test detects the impairment of liver function as frequently as any other test, and this when done along with an icterus index determination, most frequently agrees with the clinical picture.

Virgil E. Simpson, Louisville.

THORSNESS, D.T., M.D.

*The Bacteriology of Cholecystitis; the virulence and spore formation of Clostridium Welchii. S., G. and O., Vol. 59, No. 5, Nov., 1934, pp. 752-756.*

In a bacteriological study of the walls of surgically excised gall bladders in 75 cases, the following results were found: In 30 cases, the sections were sterile; streptococci were found in 13 cases, staphylococci in 26, bacillus coli in 6, diphtheroids in 5, and *Clostridium Welchii* in 5.

In human bile, 59 cases were studied. In 50 it was sterile, streptococci were found in 7, staphylococci in 1, bacillus coli in 1, bacillus subtilis in 1, and *Clostridium Welchii* in 1. In 25 cases of gall stones in man, the concretions were sterile in 15 cases, streptococci were found in 5, staphylococci in 3, bacillus coli in 4, bacillus subtilis in 1, and bacillus pyocyaneus in 1.

*Clostridium Welchii* found in gall bladders usually come from the intestinal tract and reach the gall bladder through the portal system or by ascending through the duct. The author feels as the result of the studies which he has carried out, that this organism is in the nature of a secondary invader and seldom is found to be the primary cause of cholecystitis. It is also shown that a healthy person is able to reduce *Clostridium Welchii* to a state of low virulence as well as inability to form spores and for the maintenance of virulence and spore forming ability of this organism in vivo, there must be a marked lowering of tissue resistance.

N. W. Swinton, Boston.

RIVERS, A. B.

*Pain in Benign Ulcers of Esophagus, Stomach and Small Intestine. J.A.M.A. 104:169 (Jan. 19, 1935.)*

This study concerns itself primarily with the pain mechanism in patients with peptic ulcers. The clean cut syndrome of peptic ulcer is diagnostic of uncomplicated peptic ulcer. When a peptic ulcer invades different depths of tissue or neighboring organs complicated symptoms develop. In the material used only such cases were accepted in which direct inspection of tissues and exact information from the history were obtainable.

In the esophageal ulcer group, the ulcers were situated just above the cardia. The pain was present and intensified by deglutition.

In more than 90 percent of patients with shallow gastric ulcers the pain was poorly localizable. Large ulcers or subacute inflamed ulcers gave definite pain localization in half of the cases.

Perforating gastric ulcers in 90 per cent of the cases gave accurately localizable pain in the left upper quadrant.

Obstructing duodenal ulcers produce diffuse epigastric distress. In 90 percent of perforating duodenal ulcers the pain is localized with accuracy to the right upper abdominal quadrant.

In shallow ulcers in or about a gastro-enteric stoma the pain is poorly localizable. Perforating ulcers involving a gastro-enteric stoma produced definitely localizable pain. Perforating jejunal ulcers in 96 percent of cases caused a downward or posterior projection of that pain.

Francis D. Murphy, Milwaukee.

PORTIS, SIDNEY A., AND GROVE, J. C.

*The Gastro-Intestinal Manifestations of Urologic Disease. J.A.M.A. 104:710 (Mar. 2, 1935.)*

The close anatomic relationship of the kidneys with other abdominal viscera and because of the inter-relationship of the nerve supply of the upper urinary tract and the organs of digestion, the gastro-enterologist should be prepared to discover pathological processes in the urinary tract in individuals having gastro-intestinal complaints without pathology in this tract. Especially important is the fact that although the history may reveal some urinary difficulty frequently it does not. The authors report a group of thirty patients of this type. Detailed discussion of nine of the cases is given.

The authors emphasize that in any obscure gastro-intestinal complaint the urological tract should be carefully investigated. In many of these cases the investigation will be rewarded by definite findings, which may then be treated with benefit to the patient.

Francis D. Murphy, Milwaukee.

JACKSON, CHEVALIER, AND JACKSON, CHEVALIER L.

*Peroral Gastroscopy, Including Examination of the Supradiaphragmatic Stomach. J.A.M.A. 104:269 (Jan. 26, 1935.)*

The authors discuss the three methods of gastroscopy namely the open tube, a lens system and a combination of the open tube and lens system.

The open tube is the method required for the removal of foreign bodies and the taking of specimens for histologic study. Its limitations are that it requires a straight and rigid tube, much training and skill in the introduction of the instrument and a limited explorable area.

The advantage of a lens system is that layer field of vision is available. The limitation to its use is the danger of the introduction of an instrument presenting no esophageal lumen ahead. This danger is overcome by the introduction of an open tube through which a lens system is passed.

The authors describe the normal colon, form and movements seen through the gastroscope in the esophagus and stomach.

The authors state that every patient with gastric symptoms should have a gastroscopic examination for diagnosis unless there are serious contraindications. Hematemesis, chronic gastritis, diagnosed by gastroscopy in addition to all other established diagnostic aids.

Foreign bodies that are too large to pass thru a normal or a small pylorus, or of such character as to render its passage through the intestine dangerous, should be removed by peroral gastroscopy.

In gastritis and in examination of the supradiaphragmatic stomach gastroscopy is of value.

In diagnosis of new growths and in the obtaining of biopsy specimens gastroscopy has proven valuable and free from danger.

Francis D. Murphy, Milwaukee.

## SECTION II—*Experimental Physiology*

### A Symposium Concerned with the Duodenal Factors in the Neutralization of Acid Chyme\*

By

FRANK C. MANN, M.D.,

and

JESSE L. BOLLMAN, M.D.

ROCHESTER, MINNESOTA

THE following series of papers is offered as a contribution to the problem of the physiologic mechanisms by which the normal reaction of the duodenum is maintained. Our interest in this subject has developed from our studies of experimentally produced peptic ulcer in which it appears that exposure of the intestinal mucosa to unneutralized acid for a longer period than occurs normally is a major factor in the development and maintenance of chronic peptic ulcer. In these experiments no definite increase in gastric acidity can be demonstrated, but duodenal or gastrojejunal ulcer develops following interference with the alkaline secretions of the duodenum, liver, or pancreas. These three alkalizing secretions represent the main protection of the gastro-intestinal tract against the formation of ulcer.

We would sharply differentiate two types of experimentally produced ulcerations of the gastric and intestinal mucosa. The one type of multiple hemorrhagic erosions of the mucosal surface, such as is often seen in the gastritis of terminal uremia and other toxic conditions, has been produced experimentally by various procedures. One of us described such ulcers that occur following removal of both suprarenal glands (4). Durante has described similar lesions which occur following section of the splanchnic nerves. Similar lesions have been produced by injection of diphtheria toxin and other bacterial products, after the administration of certain drugs, and by a large number of other methods. Unless death intervenes, these lesions heal promptly and completely and do not develop into lesions which resemble chronic peptic ulcers. The experimentally produced lesions that develop into peptic ulcers, which are grossly and microscopically similar to peptic ulcers as seen in man, are quite different from this acute hemorrhagic type of erosion.

The type of lesion that resembles true peptic ulcers, which is usually single and always few in number, was produced by Exalto, by Mann and Williamson and others, particularly by Matthews and Dragstedt and Weiss, by draining the duodenal content into the term-

inal portion of the ileum. Typical gastrojejunal ulcers developed after this procedure at the site where the gastric content first impinged on the jejunal mucosa. This lesion was of the perforating type, beginning with a pale, saucer-like erosion of the surface of the mucosa and gradually becoming deeper until it appeared indistinguishable from peptic ulcers as seen in man. Many subsequent methods of development of experimental peptic ulcer have been devised with this principle of surgical removal of some of the alkalizing influences of the duodenum (3).

All of these methods of forming ulcer indicate that there are at least three factors of importance in producing peptic ulcer. The acid factor appears most important. Exposure of the mucosa to unneutralized acid over a longer period than occurs normally results in the formation of ulcer and prevents the healing of the lesion. Interference with or failure of the neutralizing mechanisms appears to be of primary importance in the causation of these lesions. Mechanical factors, such as the direction of force of the contracting stomach, seem to determine the site of formation of ulcer. The individual resistance of the various tissues to the formation of ulcer also determines the situation of the experimental ulcer. The fundus of the stomach is more resistant to ulcer formation than is the pyloric mucosa, the duodenum is less resistant, and resistance decreases in the small intestine with the distance from the pylorus. Thus the formation of ulcer in these experiments appears to be the result of the amount of exposure to acid, the resistance of the tissue exposed to the acid, and of mechanical factors. Constitutional factors in formation of the ulcer are suggested by certain experiments, but these may be a part of the acid and mechanical factors. In the experiments of surgical drainage of the duodenum, the constitutional factor appears slight, since healing of the peptic ulcer occurs following surgical protection of the ulcerated area from the acid and mechanical factors, and a new ulcer will develop at a new site exposed to these two factors.

Our first attempts to study the secretions of the duodenum failed to give us data of physiologic importance. For the most part our failures were due to the

\*Division of Experimental Medicine, The Mayo Foundation.  
Submitted May 12, 1935.



development of duodenal fistulas which rapidly produced symptoms like those of high intestinal obstruction (8). Undoubtedly most of the changes in the reaction of the duodenum that we observed were the results of loss of duodenal content and could not be considered physiologic. However, we were able to develop a method of producing a duodenal fistula which did not leak and through which small samples of duodenal content could be removed at intervals with no physiologic disturbance (6). One animal with such a duodenal fistula has been in the laboratory for six years and has always been in excellent condition. With this type of fistula, subsequent operations could be performed, so that the duodenum could be isolated from the remaining portion of the gastro-intestinal tract and the biliary and pancreatic ducts transplanted or isolated. The following studies of the neutralizing effects of the duodenal secretions were made with modifications of this method.

Several facts are established from the results of these studies. Whereas the reaction of the content of isolated duodenum remains remarkably constant, that of the intact duodenum, particularly the first few centimeters, undergoes marked fluctuations. This site where duodenal ulcer develops is the chemical battleground of the gastro-intestinal tract. It is clearly established that the duodenal secretions make the duodenal content capable of neutralizing more acid than

is presented to it under physiologic conditions. The pancreatic secretion is the most important of the three secretions in maintaining the normal reaction of the duodenal content. Diversion of bile from the duodenum has practically no effect on neutralization of the acid chyme, and its effect on the reaction of the duodenal content is probably mainly due to dilution. Elimination of the pancreatic secretion from the duodenum has a slight, but under certain conditions a definite, effect on the neutralization of the gastric content passed into the duodenum. It is apparent that the normal duodenum has marked powers of compensation for the loss of one of its secretions.

We have always been impressed with the remarkable power of the stomach and the duodenum to compensate for marked alterations in their secretory mechanisms. While we have emphasized the capacity of the normal duodenum to neutralize the acids that reach it from the stomach, thus permitting an almost unvarying reaction of the content of the jejunum and ileum, it should be noted that this capacity is definitely limited, as evidenced by the increased acidity of the duodenal content following a protein meal, which is further enhanced after elimination of the secretion of the pancreas. It also appears significant that resistance to the formation of ulcer is decreased in proportion to the interference with the alkalizing mechanism of the duodenum.

#### REFERENCES

1. Durante, Luigi: The trophic element in the origin of gastric ulcer. *Surg., Gynec., and Obst.*, 22:399-406, April, 1916.
2. Exalto, J.: Ulcus jejuni nach Gastroenterostomie. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 23:13-41, 1911.
3. Harper, F. R.: Development of experimental peptic ulcer: changes in acidity and treatment. *Proc. Staff Meetings of Mayo Clinic*, 7:273-276, May 11, 1932.
4. Mann, F. C.: A study of the gastric ulcers following removal of the adrenals. *Jour. Exper. Med.*, 23:203-208, Feb., 1916.
5. Mann, F. C., and Bollman, J. L.: A method for making a satisfactory fistula at any level of the gastro-intestinal tract. *Ann. Surg.*, 93:794-797, March, 1931.
6. Mann, F. C., and Williamson, C. S.: The experimental production of peptic ulcer. *Ann. Surg.*, 77:409-422, April, 1923.
7. Matthews, W. B., and Dragstedt, L. R.: The etiology of gastric and duodenal ulcer. *Surg., Gynec., and Obst.*, 55:265-286, Sept., 1932.
8. Walters, Waltman and Bollman, J. L.: The toxemia of duodenal fistula: physiologic changes concerned in the production of its characteristic chemical reactions of the blood. *Jour. Am. Med. Assn.*, 89:1847-1853, Nov. 26, 1927.
9. Weiss, A. G.: Ulcères chroniques gastro-duodénaux expérimentaux créés par la dérivation sucs des alcalins duodénaux. *Strasbourg-méd.*, 90:549-552, Sept. 15, 1930.

## The Reaction of the Content of the Isolated Duodenum\*

By

PAT R. IMES, M.D.\*\*

ROCHESTER, MINNESOTA

THAT the secretions poured into the duodenum are normally alkaline or neutral in reaction and serve to neutralize, buffer, or dilute the acid chyme has long been recognized. In recent years alkalinity and neutralization have been accurately demonstrated in man as well as in animals. The duodenal content of the former is easily obtained through the Rehfuß tube. Experimentally, however, it has been found more advantageous to obtain the content through fistulas draining externally. The duodenal content, as obtained in either manner, is obviously usually a mixture of

gastric secretion, food, and the secretions passed into the duodenum. Two of the secretions drained into the duodenum, bile and pancreatic juice, have been obtained separately by cannulating the bile and pancreatic ducts, respectively. Determinations of the hydrogen ion concentration and the buffer values of these two secretions have therefore been made (2). Figures are not available for the reaction of the duodenal content unmixed with the gastric content that passes the pylorus. The purpose of this investigation was to determine the changes in pH and buffering values of the duodenal content of the isolated duodenum.

In order to obtain the duodenal content under as nearly physiologic conditions as possible, duodenal fis-

\*Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science.

\*\*Fellow in Surgery, University of Minnesota, Rochester, Minnesota. Now residing in Louisville, Kentucky. Submitted May 12, 1935.

tulas were made in six healthy dogs using the transposed intestinal loop method (4). At a subsequent second-stage operation the stomach was separated from the duodenum and anastomosed to a loop of jejunum about 25 cm. from the closed end of the duodenum (Fig. 1). All operations were done with the animals under ether anesthesia and using surgical technic. Following this procedure samples of the content of the isolated duodenum were easily obtained and their hydrogen ion concentrations determined using the quinhydrone gold electrode. The buffering capa-

city of the duodenal content was also determined on the samples obtained from one of the animals. This was done by taking 2 cc. of the secretions and adding tenth-normal hydrochloric acid until the pH was reduced to from 3.5 to 4.0, which level represents the end point of dimethyl-amino-azobenzene as used in determining the free acidity of gastric secretions. Thus the degrees of alkalinity are analogous to the manner commonly used to express the acidity of the gastric secretions. The potentiometer was used to determine when that pH level was reached.

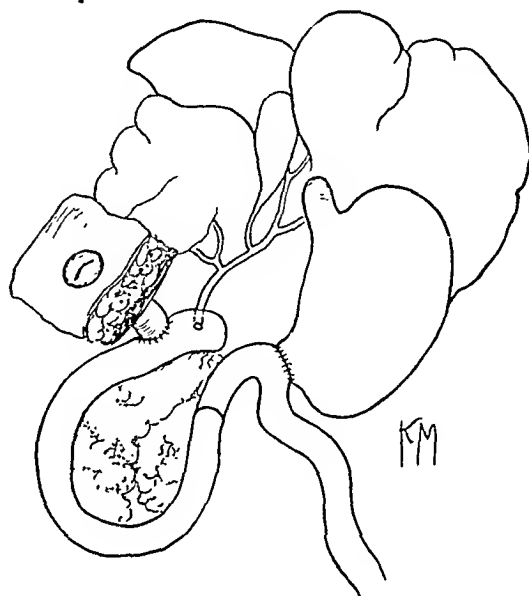
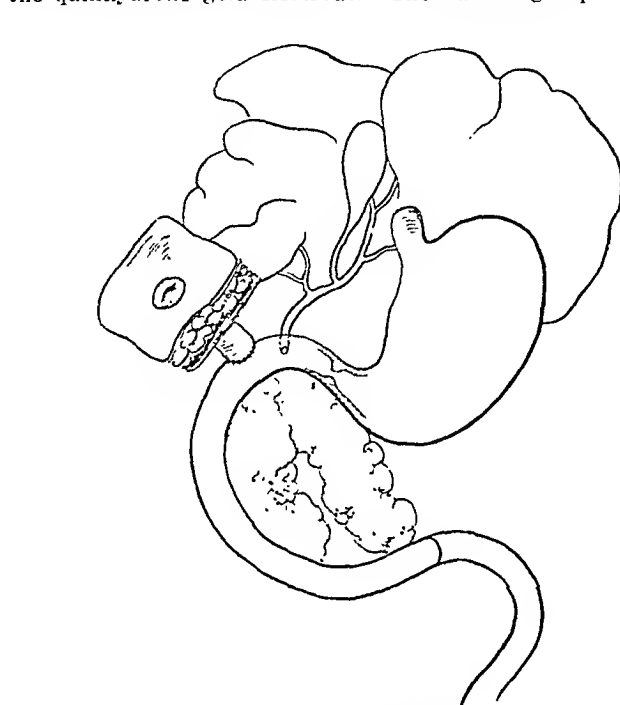


Fig. 1. Relative position of duodenal fistula and isolated duodenum.

city of the duodenal content was also determined on the samples obtained from one of the animals. This was done by taking 2 cc. of the secretions and adding tenth-normal hydrochloric acid until the pH was reduced to from 3.5 to 4.0, which level represents the end point of dimethyl-amino-azobenzene as used in determining the free acidity of gastric secretions. Thus the degrees of alkalinity are analogous to the manner commonly used to express the acidity of the gastric secretions. The potentiometer was used to determine when that pH level was reached.

Samples of the duodenal content were secured at half-hour intervals on animals during the fasting state and following the ingestion of the following standard meals: 100 gm. of lean horse meat, 200 gm. of lean horse meat, 100 gm. of lard mixed with 100 gm. of cracker meal, and 100 gm. of syrup mixed with 500 cc. of milk. Observations were made in two series, before and after isolating the duodenum.

### RESULTS

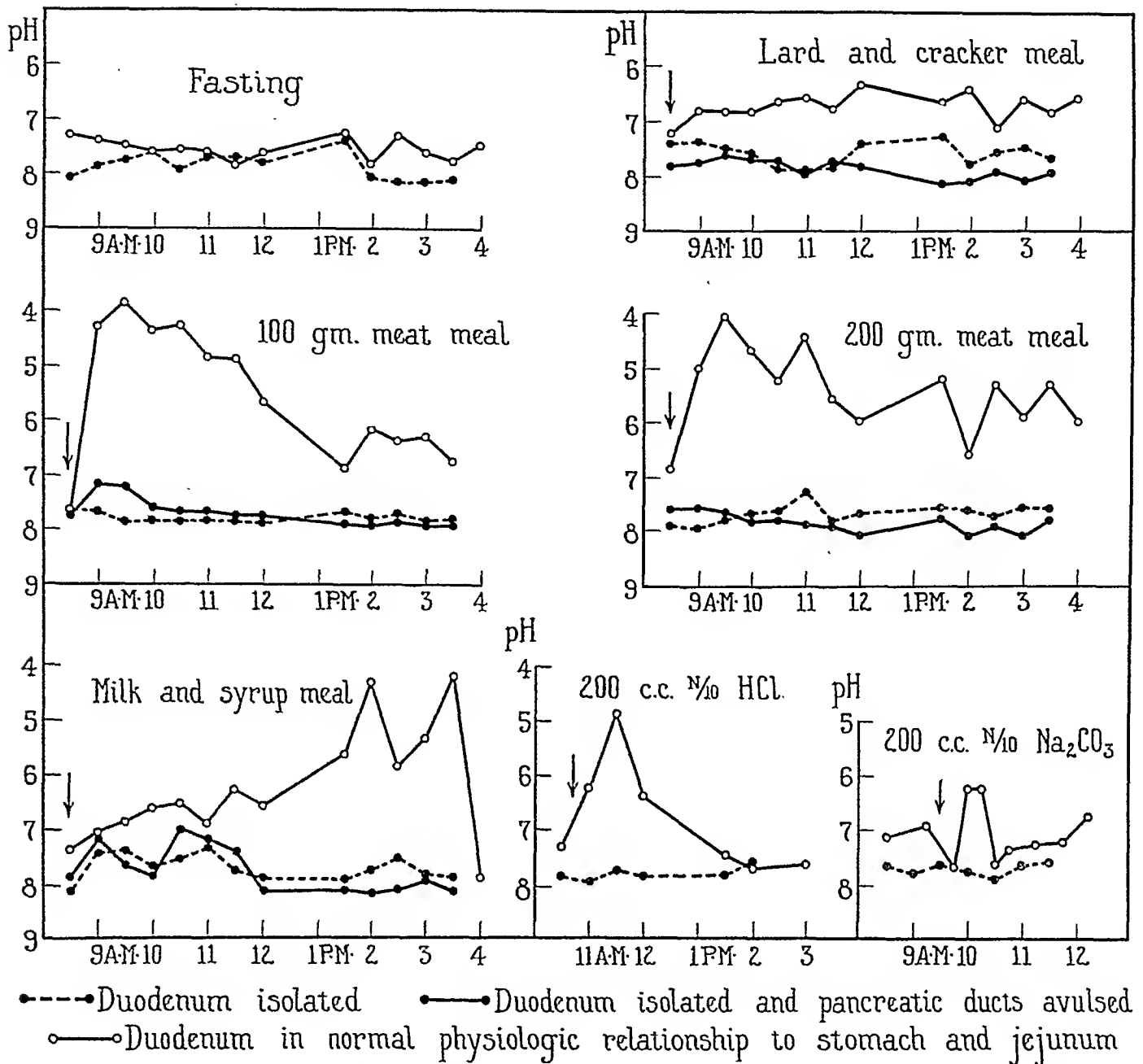
The first series of determinations on the duodenal content, with the duodenum in normal physiologic relationship to the stomach, confirm the results of Mann and Bollman (3) who worked under identical conditions and used a similar method. The reaction of the fasting content was regularly alkaline, the pH varying

from 7.00 to 7.88 except for an occasional sample as low as 5.64. Following test meals, the pH fell almost immediately and usually maintained a fairly characteristic curve throughout the eight-hour period of observation for each type of test diet. Following the fat meal, the pH was lowered to between 6.0 and 7.0 and maintained that level throughout except for an occasional sample from one of the animals which was as low as 2.0. A somewhat similar curve was obtained following a carbohydrate meal; however, in several instances, there was a definite tendency toward a de-

crease in the pH after a period of three or four hours following this meal, and that low level was maintained usually for the remainder of the period of observation. Following a protein meal, the samples were definitely more acid than with the other diets, the pH ranging between 3.5 and 5.0, with occasional variations between 2.2 and 6.75. That low level was maintained longer when feedings consisted of 200 gm. of raw meat than when only 100 gm. were given. Following the latter meal the pH began to approach the fasting level in five to six hours following feeding.

The second series of determinations, on the reaction of the content of the isolated duodenum composed of bile, pancreatic juice, and succus entericus, was made on samples obtained under conditions identical with the first. Regardless of the state of alimentation or the type of test diet used, the pH was remarkably constant and varied between 7.10 and 8.15 with few exceptions. Samples of the duodenal content following the administration of 200 cc. of tenth-normal hydrochloric acid and 200 cc. of tenth-normal sodium carbonate likewise showed no appreciable variation in the hydrogen ion concentration (Fig. 2).

The buffer values of the content of the isolated duodenum, however, showed marked variation, 40 to 95 points, and usually were directly proportional to the



pH of the original sample although frequently just the opposite was noted. Thus a sample with a pH of 8.0 might have 80 points (40 and 80 cc. of tenth-normal hydrochloric acid required to reduce the pH of 100 cc. of the secretions to 4.0). The state of alimentation and the various test diets had no constant effect on the buffer capacity of the samples of duodenal content. Two of the animals were given 1 mg. of histamine, which did not affect the pH or buffer capacity of the duodenal content; likewise, samples following the administration of 200 cc. of tenth-normal hydrochloric acid and 200 cc. of tenth-normal sodium carbonate showed no consistent changes.

The influence of the pancreatic secretion on the pH and buffer capacity of the content of the isolated duodenum was studied by evulsing the pancreatic ducts and comparing the determinations made before and

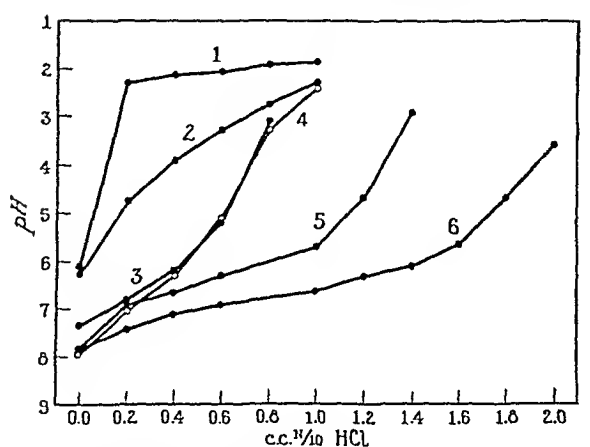
Fig. 2. Representative curves of pH of the content of the intact and isolated duodenum in the fasting state and following various test meals.

after evulsion. A study of the effect of this procedure on the content of the intact duodenum was made by Hoerner. Following evulsion of the pancreatic ducts,

the pH of the duodenal content was essentially unchanged, the pH being 7.17 to 8.13 as compared to 7.0 to 8.15 before evulsion. The buffer values, however, were definitely reduced and amounted to approximately two-thirds of those before evulsion, an average of 37 points as compared with 60 points before evulsion (Fig. 3).

#### COMMENT

Much work has been done on the reaction of the content of the duodenum in its normal anatomic and physiologic relationship with the stomach, and some work has been done on the reaction of pancreatic and biliary secretions as obtained by draining externally through cannulas. However, this investigation had to



- 1-Distilled water  
 2-Bile (fresh) from gallbladder (removed surgically)  
 3-Bile obtained from common duct fistula  
 4-Duodenal secretions after pancreatic duct avulsion  
 5-Average from combined duodenal secretions  
 6-Maximum from combined duodenal secretions

Fig. 3

do with the reaction and degree of alkalinity of the isolated duodenal content as a whole, when obtained under approximately physiologic conditions.

The constancy of the slightly alkaline reaction of the content of the isolated duodenum in contrast to the highly variable reaction of the gastric secretion is explained by the presence of weak alkalies, buffer substances, in the former. Consequently, determination of the pH alone gave no reliable indication as to the degree of the alkalinity, and the latter, as determined

Fig. 3. Curves illustrating the buffer capacity of various secretions obtained by adding tenth-normal hydrochloric acid to 2 cc. of the secretion in amounts as indicated.

by titration, was found to fluctuate in rather wide limits. This qualitative fluctuation is dependent on the relative proportion of pancreatic juice, bile, and duodenal secretion in a given sample and bears no relationship to the state of alimentation. There is, however, a quantitative relationship to the state of alimentation, which was only grossly observed, and no accurate estimation of the total amount of alkali secreted could be determined.

The degree of alkalinity of the combined duodenal secretions is equal to, and usually exceeds, the degree of acidity of the gastric secretions when expressed in terms of titration for equal amounts. Thus, the protective function of the duodenal secretions in preventing free hydrochloric acid from coming in contact with the small intestine is established in a concrete manner. Without this protection, McCann observed an increasing tendency to ulceration that was directly proportional to the alkaline deficit beyond the pylorus.

#### SUMMARY

The reaction of the content of the isolated duodenum is alkaline, with a pH of from 7.10 to 8.15. The alkalinity is caused by weak alkalies or buffer substances which fluctuate quantitatively. This fluctuation in reaction of the duodenal content probably depends on the relative proportions of its major constituents: pancreatic juice, bile, and duodenal secretion. The pancreatic juice has approximately twice the alkalinity of the bile.

#### REFERENCES

1. Hoerner, M. T.: The effect of exclusion of the pancreatic secretion by evulsion of the pancreatic ducts on the reaction of the duodenal content. *Am. Jour. Digest. Dis.* (In press).
2. Jones, K. K.: A comparison of the buffer value of bile and pancreatic juice secreted simultaneously. *Proc. Soc. Exper. Biol. and Med.*, 28:567-568 (Mar.) 1931.
3. Mann, F. C. and Bollman, J. L.: The reaction of the content of the gastro-intestinal tract. *Jour. Am. Med. Assoc.*, 95:1722-1724 (Dec. 6) 1930.
4. Mann, F. C. and Bollman, J. L.: A method for making a satisfactory fistula at any level of the gastro-intestinal tract. *Ann. Surg.*, 93:794-797 (Mar.) 1931.
5. McCann, J. C.: Experimental peptic ulcer. *Arch. Surg.*, 19:600-659 (Oct.) 1929.

## The Capacity of the Duodenum to Neutralize, Buffer and to Dilute Acid\*

By

G. ARNOLD STEVENS, M.D.  
 ROCHESTER, MINNESOTA

THERE have been numerous studies of the reaction and buffering capacity of the content of the intact duodenum. In these studies it obviously was not possible to quantitate the duodenal content in this respect because of the admixture of saliva, food, and gastric secretion entering the duodenum through the pylorus. On the other hand, similar investigations of

the isolated duodenum which obviate this error, performed in vitro, have been few, and quantitative determination of the capacity of such a duodenum in vivo has not been reported.

It was the object of this investigation to accomplish this in the following manner: Fistulous openings were established at each end of the duodenum of dogs. The duodenum was subsequently isolated, thus preventing the influx of gastric content. Hydrochloric acid, of a strength within physiologic limits, was passed into the upper opening and the pH of the con-

\*Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M. S. in Surgery. Fellow in Surgery, The Mayo Foundation, Rochester, Minnesota. Submitted, May 12, 1935.

tent obtained from the caudal fistula determined. This procedure was carried out before and after isolation of the duodenum, in the fasting state and after the ingestion of various diets. From the data obtained it was possible to estimate the maximal capacity of the duodenum to neutralize, buffer, and dilute the acid introduced through the fistula and to suggest a relationship between the amount of acid normally passing through the pylorus and this capacity of the duodenum.

### REVIEW OF LITERATURE

Reports of the reaction of the duodenal content as a whole have not been in accord. McClendon and others believed that variations in types of indicators and attempts to harmonize results in vivo and in vitro are largely responsible for erroneous deductions. Mann and Bollman (12), using a transposed loop of intestine in making the fistula and the electrometric method of hydrogen ion determination, found values that

sodium, potassium, and calcium. They found that chloride ion, bicarbonate ion, and a trace of phosphate constituted the acid factors. Jones, Apperly, and others stated that the essential alkali of the pancreatic juice and bile is sodium bicarbonate, values being quoted of 0.65 per cent for the former and 0.2 per cent for the latter. Howell remarked that the alkaline reaction of the succus entericus is due to this salt.

Boyden and Birch attempted to ascertain in some measure the neutralizing power of the duodenal content of man. They found that various amounts of acid of physiologic strengths introduced through the Reh-fuss tube were neutralized in four to sixteen minutes. Spontaneous spurts of acid as a result of opening of the pylorus were said to be neutralized in thirteen minutes.

### METHOD OF INVESTIGATION

This investigation was conducted with seven healthy dogs weighing from 8.1 to 21.8 kg.

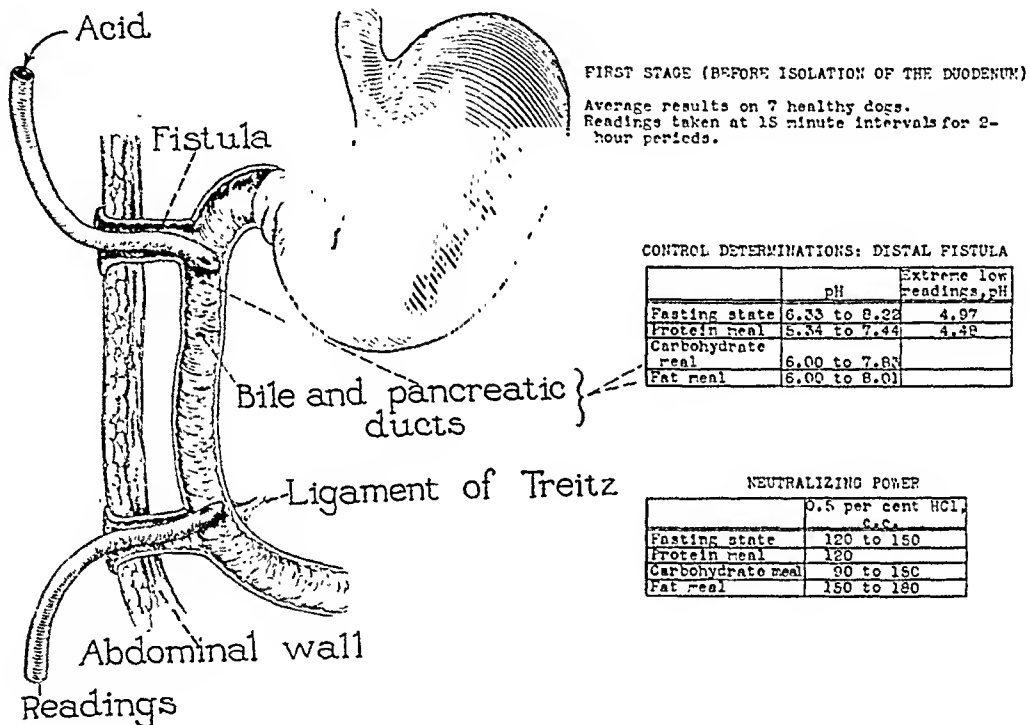


Fig. 1. Method of administration and collection of solutions exposed to duodenal action. The neutralizing power indicates the volume of hydrochloric acid that may be introduced into the duodenum in two hours without changing the pH of the fluid from the distal end of the duodenum.

seemed representative of results of the more recent workers. The pH of the content of the duodenum of the fasting dog averaged 7.6, with occasional fluctuations from 5.6 to 2. After a meal, the pH of the duodenal content paralleled that of the gastric content and usually did not return to the average fasting level of 7.6 for six hours postprandially.

Results of studies of the buffer values of the duodenal content have varied. McClure, Montague, and Campbell found that 140 to 392 cc. of tenth-normal acid or alkali were required to bring 1,000 cc. of duodenal content to the neutral point. Jones observed that 1 to 6 cc. of tenth-normal hydrochloric acid would bring the reaction of 10 cc. of bile or pancreatic juice to a pH of 7.00.

Gamble and McIver (5) determined that the fixed base of the pancreatic juice consists essentially of

Operative procedures were accomplished in two stages: The first stage (Fig. 1) consisted of making two intestinal fistulas of the transposed intestinal loop type (11), one into the duodenum just below the

pylorus and the other into the duodenum at the ligament of Treitz or into the jejunum a few centimeters caudalward. All operations were done with the animals under ether anesthesia using surgical technic.

Two weeks or more elapsed after operation before observations were made on the animals. The dogs were fasted eighteen to twenty-four hours prior to each experiment. Studies were made in the fasting state and after the ingestion of the various standard meals. The diets administered consisted of 200 gm. of ground lean meat, a mixture of 300 cc. of milk and 200 cc. of syrup, 125 gm. of lard and 75 gm. of crackers, and 200 gm. of fresh horse fat, respectively. The

dogs were found to ingest this last more readily than the other type of fat meal.

Specimens were removed by soft rubber catheters through both proximal and caudal fistulas at intervals of a half hour and the pH values were ascertained. This procedure was usually repeated on two or three different days for each diet. The pH was determined with the quinhydrone gold electrode.

After establishing these control readings, studies on the effect of injection of acid on the reaction of the duodenal content were made. The dogs were trained to lie quietly without restraint on specially arranged stands during intervals required for the observation. Five-tenths per cent hydrochloric acid was introduced continuously at a fixed rate by the gravity drip method through rubber tubing connected to a catheter in the

denal end inverted. The proximal end of the pylorus was anastomosed to the jejunum to restore the continuity of the gastro-intestinal tract. The distance from the site of the anastomosis to the opening of the caudal fistula was usually about 30 cm.

The studies which were performed before the pylorus was cut off from the duodenum were repeated on the isolated duodenum (Fig. 2).

RESULTS

**DUODENUM INTACT.**—The reaction of the duodenal content obtained through the proximal fistulas of fast-ing dogs was usually within a range of 6.15 to 8.15, with an occasional lowering to 2.59, whereas that obtained through the caudal fistulas ranged from 6.33 to 8.22, with an extreme acidity of 4.97.

SECOND STAGE (AFTER ISOLATION OF THE DUODENUM)

Average results on 7 healthy dogs.  
Readings taken at 15 minute intervals for 2-  
hour periods.

CONTROL READINGS: DISTAL FISTULA

|                      | pH           | Extreme low<br>readings, pH |
|----------------------|--------------|-----------------------------|
| Fasting state        | 7.07 to 8.11 |                             |
| Protein meal         | 7.00 to 8.18 | 6.63                        |
| Carbohydrate<br>meal | 7.00 to 8.01 |                             |
| Fat meal             | 7.00 to 8.01 |                             |

NEUTRALIZING POWER

|                      | 0.5 per cent HCl,<br>C.C. |
|----------------------|---------------------------|
| Fasting state        | 150 to 180                |
| Protein meal         | 180 to 210                |
| Carbohydrate<br>meal | 180 to 210                |
| Fat meal             | 180 to 210                |

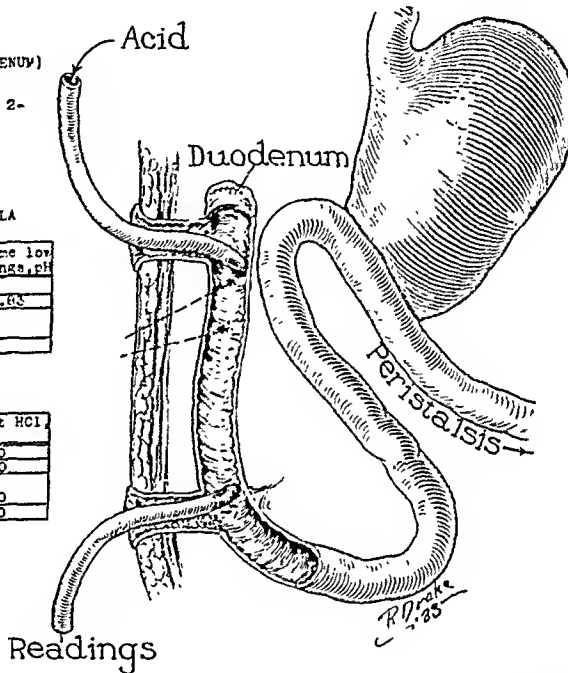


Fig. 2. Method of administration of solutions to the isolated duodenum... The neutralizing power indicates the volume of hydrochloric acid that may be introduced into the duodenum in two hours without changing the pH of the fluid from the distal end of the duodenum.

proximal fistula, (Fig. 1). The pH of specimens collected from the distal fistula every fifteen minutes for a two-hour period was determined. Such a procedure was repeated on separate days until a determination of the maximal amount of acid that could be introduced into the proximal end of the duodenum without materially changing the reaction of the content of the distal portion was made. This was considered to be the capacity of the duodenum to neutralize, buffer, and dilute acid under the particular conditions that obtained.

Quantitative determinations of chloride ion were made before and after the ingestion of diets to estimate the amounts of buffered as well as unbuffered acid escaping through the pylorus with each type of meal. Similar studies were conducted before and after introduction of hydrochloric acid to approximate the portion of the latter that was actually buffered.

The second stage operation consisted of isolation of the proximal end of the duodenum (Fig. 2). To accomplish this the pylorus was sectioned and the duo-

The reaction of the content of the lower end of the duodenum for a two-hour period following the fat and carbohydrate meals did not differ materially from the fasting values. The readings after the carbohydrate meal ranged from 6.00 to 7.83, and following ingestion of the fat diets from 6.66 to 8.01. Bizarre fluctuations practically never occurred.

More acid values obtained with the protein meal. The hydrogen ion concentration varied from 5.34 to 7.44 in most instances, with occasional low readings of 4.48.

The chloride ion level of the content of the distal end of the duodenum was lowest after fat and carbohydrate meals and highest following the meat diet. With the two animals studied in this regard a slight decrease in chloride content occurred after ingestion of horse fat. Before the meal, values of 2.60 and 1.70 mg. of chloride ion per cc. of duodenal content were obtained, whereas for two hours after the fat was eaten average figures of 2.11 and 1.58, respectively,



were noted. After the meat meal, on the other hand, an increase in the chloride level was evident. The readings before the meal were 1.45 and 1.80, with a rise to 2.79 and 2.50, respectively, afterward. Similar determinations with the carbohydrate diet yielded inconsistent results.

Fasting levels of chloride ion in the other dogs ranged from individual averages of 1.43 to 3.06 mg. per cc. of duodenal content obtained through the distal fistula.

The appearance of specimens removed varied in fasting animals. Pale secretions of the pancreatic type, light yellow samples the color of hepatic bile, and deep yellow or brown fluid considered characteristic of gallbladder bile were obtained. These were either clear and thin or cloudy and viscid and usually contained considerable mucus. Within fifteen to thirty minutes after meals the duodenal content usually assumed the color, characteristic of the particular diet, namely, dark yellow or brown after meat, light yellow (with curds) after milk and syrup, and light yellow after fat. Specimens of the last were usually of a creamy consistency and would often solidify on standing over night in a cool place. Not infrequently, however, clear samples, resembling those obtained from fasting dogs, were obtained after feedings.

The neutralizing capacity of the duodenum, as determined by the continuous introduction of acid for two-hour periods, ranged from 1 to 1.5 cc. of 0.5 per cent hydrochloric acid per minute (1440 to 2160, or an average of 1800 cc. per day) in the various fasting animals. Following the carbohydrate meal, this capacity usually did not differ materially from that with the animals in a fasting state. The capacity of the various dogs ranged from 0.75 to 1.25 cc. of 0.5 per cent hydrochloric acid per minute. The administration of the protein meal usually resulted in a lowering of the neutralizing capacity by about 0.25 cc. per minute of the 0.5 per cent acid, although in one animal no difference from the figure obtained in the fasting state was noted.

Contrary to these findings, all but one of the animals, after receiving a fat meal, showed a capacity to neutralize an average of 0.25 cc. per minute more than with the other diets. The one dog which neutralized equal amounts of acid when in a fasting state and following a fat meal received the diet of 125 gm. of lard and 75 gm. of crackers. All of the others except one were given 200 gm. of horse fat.

The chloride content of the duodenal specimens, removed from fasting animals receiving amounts of acid continuously neutralized, was materially greater than the fasting control level. The average determinations of the different animals varied from 2.60 to 2.87 mg. per cc. of duodenal content.

**DUODENUM ISOLATED.**—The pH of the duodenal content obtained from each fistula remained within limits of 7.00 to 8.25 regardless of diet or state of alimentation with the exception of one animal in which an extreme distal fistula reading of 6.59 occurred.

Individual chloride averages of 1.13 to 2.37 mg. per cc. of duodenal content obtained.

In fasting animals it was usually not possible to secure specimens in quantities of more than 1 to 2 cc.

Indeed, at times, no sample could be removed. The fluid obtained was usually pale, or light to dark yellow, and was either thin or of mucous consistency. On the other hand, within three to five minutes or more after food of any type entered the stomach, amounts of from 3 to 6 cc. of duodenal contents could invariably be obtained. These specimens were usually relatively clear and the color had no consistent relationship to the type of meal ingested. Reflux of stomach content from the jejunal loop was an unusual occurrence. In fact this was noted on an average of but once in approximately fifteen specimens taken at half hour intervals. After permitting the dogs merely to smell meat, increases of only 1 to 2 cc. in the available quantity of duodenal secretions was noted.

The neutralizing capacity of the isolated duodenum of fasting animals was 1.5 to 1.75 cc. of 0.5 per cent hydrochloric acid per minute (2160 to 2520, or an average of 2340 cc. per day) for two-hour periods. This was equivalent to, or but slightly in excess of, the capacity of the intact duodenum during the same intervals following a meal of horse fat but was 0.25 to 0.5 cc. per minute (360 to 720, or an average of 540 cc. per day) more than when other conditions obtained in the dogs prior to isolation of the duodenum. The neutralizing capacity for similar durations following all diets was usually 0.25 cc. per minute greater than that of the fasting dogs. The average chloride content of specimens collected during the administration of acid was elevated to levels of 2.34 to 3.8 mg. per cc.

The two-hour neutralizing capacity in the fasting state of 1.75 cc. of 0.5 per cent hydrochloric acid per minute of two dogs was found to be maintained for twenty-four hours. Samples collected at half-hour intervals were neutralized with but few exceptions. From the observations on one of the animals, which received 200 gm. of lean meat every four hours, it appeared that the slight increase in neutralizing power of the isolated duodenum following meals subsided within two to three hours. After the first meat meal, subsequent four-hour feedings produced no evident change in neutralizing capacity.

Following the introduction of 0.15 per cent hydrochloric acid, continuously for two-hour periods, it was found that the same number of grams of hydrochloric acid was neutralized as with the introduction of 0.5 per cent acid.

Samples collected after the introduction of single amounts (10 to 100 cc.) of fifth to twentieth normal acid showed complete neutralization, no elevation of the chloride level, and absence of free hydrochloric acid in four to ten minutes. An increase in duodenal content was noted for an hour after the introduction of acid.

## RESULTS OF STUDIES PERFORMED IN VITRO

In vitro, approximately three parts of duodenal content obtained ten minutes after the introduction of acid ceased neutralized 1 part of 0.5 per cent hydrochloric acid. Specimens (6 cc. obtained from two dogs on which only second stage studies were made), having reactions of pH 7.51 and 7.68, mixed with 2 cc. of 0.5 per cent acid had resultant hydrogen ion concentration of 6.83, and 7.07, respectively.

The addition of equal parts of duodenal content with a pH of 5.64 to the fat, protein and carbohydrate

meals brought about the respective reactions: 6.63, 6.00, and 6.00.

### COMMENT

A possible source of error in this study is the occasional reflux of gastric content through the jejunal loop into the duodenum. This could not be completely excluded; however, as has been previously stated, it occurred so infrequently (once in fifteen readings) that it cannot be considered an important error. Complete isolation of the duodenum obviously would have prevented this source of error, but, as Walters and Bollman, Gamble and McIver (4), and others have pointed out, the resulting loss of duodenal secretions, especially that of the pancreas, is incompatible with prolonged life of the animal. On the other hand, the operative procedures used in this study, although not truly physiologic, were found to be consistent with maintenance of a well nourished and apparently healthy state in the dogs used. It seems, therefore, that from such a standpoint the results of this investigation may be deemed reasonably valid.

Although transient acid reactions occurred at the caudal end of the intact duodenum of fasting animals, these fluctuations were more marked in the upper portion, namely the ulcer-forming region. Such a finding fits in with the conception of acidity being a factor in the occurrence of peptic ulcers in this region. The more acid readings following meat meals appear referable to an increased secretion of hydrochloric acid in the stomach in excess of the buffering capacity of protein. The appreciable increase in chlorides of the duodenal content after these meals substantiates such a deduction.

The same reasoning applies conversely to the more uniform alkalinity occurring after fat meals. The low chloride levels of the fatty specimens of duodenal content obtained following this type of diet indicates a minimal secretion of acid in the stomach. This finding is in accord with the current conception of the effect of a fat diet on gastric secretion. Hebert, working in this laboratory, found negligible amounts of free hydrochloric acid in the stomach of dogs with gastric fistulas two hours after ingestion of the horse fat meal used in this study. Vanzant noted that feeding ulcer patients oil in the evening prevented the characteristic nocturnal rise of acidity. Graham and Emery, Kosaka, Lim, Ling and Liu report inhibition of the secretion of gastric acid by fat.

It seems reasonable to assume that the somewhat greater neutralizing power of the duodenum with fat meals and the slight decrease in this function following meat diets is likewise attributable to lesser and greater amounts, respectively, of acid that could be introduced through the upper fistula without changing the reaction at the lower end of the duodenum. Furthermore, such results were not found after isolation of the duodenum.

The part played by the buffering qualities of the various diets used in this study is problematical. The uniform reaction of the isolated duodenum supports the belief that the transient acid fluctuations occurring in the intact duodenum are the result of spurts of gastric content passing through the pylorus.

The somewhat higher neutralizing capacity that occurs for a short time after meals in the isolated duodenum seems to be essentially the result of an augmented flow of the secretions poured into the

duodenum incident to the presence of food in the stomach. It is possible that gastric chyme coming in contact with the jejunal mucosa at the site of a gastrojejunal stoma would liberate sufficient secretin to produce this effect. Winton and Bayliss stated that the pancreas responds to reflex vagus stimulation. They remarked that the pancreatic secretion occurring a few minutes after taking food, before any chyme could reach the duodenum, is abolished by cutting the vagus nerves. These workers believed that such a secretion results from psychic stimulation. Puestow observed a "psychic" secretion of bile, lasting one to three minutes, and an increased flow of bile was noted in the isolated segments of the duodenum of dogs for three to four hours after meals. The dogs used in the present investigation, however, showed but little increase in duodenal secretion after seeing and smelling food. It appears that the duodenum responds similarly to strengths of acid in the range of 0.15 per cent to 0.5 per cent, since an equal number of grams of hydrochloric acid introduced in these dilutions was neutralized, buffered, and diluted.

The question of whether acid is absorbed in the duodenum seems clarified in some measure by the chloride determinations. In view of the material increases in the chloride level of the duodenal content following the continuous introduction of acid in relatively small amounts, it appears that most of the acid is buffered and that the absorption of hydrochloric acid, as such, in the duodenum is negligible, although it must be recognized that the chloride content of the three secretions found in the duodenum may be a source of error.

A 0.5 per cent hydrochloric acid solution could be injected into the proximal end of the intact duodenum at a rate varying from 1 to 1.5 cc. per minute for a two-hour interval without altering the reactions of the duodenal content obtained from the distal end of the duodenum. If it is assumed that the injection could be maintained for a twenty-four hour period at the same rate, the duodenum could maintain a normal reaction of its content as expelled into the jejunum after receiving 1800 cc. of 0.5 per cent acid per day. The capacity of the isolated duodenum was 1.5 to 1.75 cc. of 0.5 per cent hydrochloric acid per minute, or an average of 2340 cc. for a twenty-four hour period. According to Dragstedt and Ellis, the isolated stomach of the dog will secrete an average of 1800 cc. of 0.45 to 0.5 per cent hydrochloric acid per day. From these figures it would appear that although a considerable amount of acid reaches the duodenum in the gastric content, a larger amount of the acid produced in the stomach is neutralized, buffered, and diluted before it is expelled into the duodenum.

The determination that the duodenum before isolation is capable of neutralizing an average of 1800 cc. of 0.5 per cent hydrochloric acid in twenty-four hours, in addition to the acid passing through the pylorus, suggests that the duodenum, like the liver, kidney, and other viscera, has a reserve function in this respect considerably in excess of physiologic needs.

### SUMMARY AND CONCLUSIONS

An effort was made in this study to ascertain the actual capacity of the duodenum to neutralize, buffer, and dilute acid. Fistulous openings were made at each end of the duodenum in dogs. Control hydrogen ion determinations of the duodenal content obtained

through the fistulas were made. Acid of a strength within physiologic limits was introduced through the proximal fistula and the reaction of specimens of duodenal content removed through the distal fistula was determined. The chloride level of the duodenal content before and after standard meals and the introduction of acid was likewise estimated. The duodenum was subsequently isolated to prevent influx of gastric content and similar studies were performed.

From the results obtained certain deductions seem justified: 1. Before isolation, an apparent slight increase in the neutralizing capacity of the duodenum following ingestion of a fat meal, and the usual decrease noted after a protein meal, seem attributable

to inhibition and stimulation, respectively, of gastric secretion. 2. A transient increase in neutralizing capacity of the isolated duodenum following meals seems to be the result of an augmented flow of the secretions poured into the duodenum incident to the presence of food in the stomach. 3. It appears that acid introduced continuously in relatively small amounts is largely neutralized, buffered, and diluted, and that the absorption of hydrochloric acid, as such, in the duodenum is negligible. 4. Acid introduced in large single injections is quickly swept through the duodenum by peristalsis. 5. The duodenum has a reserve function to neutralize acid materially in excess of physiologic needs.

### REFERENCES

1. Apperly, F. L.: Duodenal regurgitation and the control of the pylorus. *Brit. Jour. Exper. Path.*, 7:111-120 (June) 1926.
2. Boyden, E. A. and Birch, A. L.: Reaction of gallbladder to stimulation of gastro-intestinal tract. 1. Response to substances injected into the duodenum. *Am. Jour. Physiol.*, 92:287-300 (Mar.) 1930.
3. Dragstedt, L. R. and Ellis, J. C.: The fatal effect of total loss of gastric juice. *Am. Jour. Physiol.*, 93:407-416 (June) 1930.
4. Gamble, J. L. and Melver, M. A.: Body fluid changes due to continued loss of the external secretion of the pancreas. *Jour. Exper. Med.*, 48:855-869 (Dec.) 1928.
5. Gamble, J. L. and Melver, M. A.: Acid-base composition of pancreatic secretion. *Jour. Exper. Med.*, 48:849-857 (Dec.) 1928.
6. Graham, W. R. and Emery, E. S., Jr.: The reaction of the intestinal contents of dogs fed on different diets. *Jour. Lab. and Clin. Med.*, 13:1097-1108 (Sept.) 1928.
7. Hebert, Warren: Personal communication to the author.
8. Howell, W. H.: Textbook on physiology. Philadelphia, W. B. Saunders Company, 1918, 799 pp.
9. Jones, K. K.: A comparison of the buffer value of bile and pancreatic juice secreted simultaneously. *Proc. Sec. Exper. Biol. and Med.*, 28:567-568 (Mar.) 1931.
10. Kosaka, T., Lim, R. K. S., Ling, S. M. and Liu, A. C.: On mechanism of inhibition of gastric secretion by fat. Gastric-inhibitory agent obtained from intestinal mucosa. *Chinese Jour. Physiol.*, 6:107-126 (Feb. 15) 1932.
11. Mann, F. C. and Bollman, J. L.: A method for making a satisfactory fistula at any level of the gastro-intestinal tract and surgery. *Ann. Surg.*, 93:794-797 (Mar.) 1931.
12. Mann, F. C. and Bollman, J. L.: The reaction of content of the gastro-intestinal tract. *J. A. M. A.*, 95:1722-1724 (Dec. 6) 1930.
13. McClendon, J. F., Bissel, F. S., Lowe, E. K. and Meyer, P. F.: Hydrogen-ion concentration of the contents of the small intestine. *Jour. Am. Med. Assn.*, 75:1638-1641 (Dec. 11) 1920.
14. McClure, C. W., Montague, O. C. and Campbell, L. L.: The pH and buffer values of duodenal contents derived from normal men. *Arch. Int. Med.*, 33:525-532, (Apr.) 1924.
15. Puestow, C. B.: The discharge of bile into the duodenum: an experimental study. *Arch. Surg.*, 23:1013-1029 (Dec.) 1931.
16. Vanzant, Frances R.: Personal communication to the author.
17. Walters, Waltman and Bollman, J. L.: The toxemia of duodenal fistula: Physiologic changes concerned in the production of its characteristic chemical reaction of the blood. *Jour. Am. Med. Assn.*, 59:1847-1853 (Nov. 26) 1927.
18. Winton, F. R. and Bayliss, L. E.: Human physiology. Philadelphia, Blakiston's Son and Company, pp. 251-252, 1931.

## The Reaction of the Duodenal Content After Exclusion of Bile from the Duodenum\*

By

JERRY W. McROBERTS, M.D.\*\*

ROCHESTER, MINNESOTA

IT was the purpose of this investigation to determine the effect of loss of bile on the reaction of the duodenal content. The ranges in reaction of the duodenal content of normal dogs during fasting and after the ingestion of various test meals were obtained. A biliary fistula was then made and the observations were repeated.

### METHODS OF EXPERIMENTATION

The necessary duodenal fistula, using the transposed intestinal loop method (2), was made in each animal and the usual postoperative care was instituted. All operations were done with animals under ether anesthesia and using surgical technic. The first series of

observations were made about two weeks after operation for duodenal fistula. The animals were fasted for twenty-four hours before each test. A specimen of the duodenal content of the fasting animal was obtained. One of the following four standard test meals was then given: 100 gm. of lean horse meat, 200 gm. of lean horse meat, 100 gm. of lard mixed with 100 gm. of cracker meal, and 100 gm. of syrup mixed with 500 cc. of milk. Specimens of duodenal content were removed and the pH determined every half hour following the ingestion of the test meal for a period of seven hours. Observations were made three times with each of the test meals. The hydrogen ion concentration of the duodenal content was determined with the quinhydrone gold electrode.

When the variation in pH of the duodenal content following each meal was established for each animal, a biliary fistula was made using the method devised by

\*Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M. S. in Surgery.

\*\*Fellow in Surgery, The Mayo Foundation, Rochester, Minnesota. Now residing in Montreal, Quebec, Canada.  
Submitted, May 12, 1935.

Rous and McMaster. Four or five days after making this biliary fistula a second series of observations was begun and the reactions of the duodenal content during fasting and after the ingestion of the test meals were determined.

## RESULTS

*Normal reaction of the duodenal content.*—The ranges in pH of the duodenal content of normal animals were in general similar to those reported by Mann and Bollman (3) and in the preceding paper (1). The reaction of the specimen of duodenal content obtained after twenty-four hours of fasting was usually slightly alkaline. In eighty fasting specimens, the extreme readings were pH 4.68 and pH 7.83. The reaction of the specimens obtained from three dogs every half-hour from twenty-four to thirty-one hours of fasting indicated a narrow range of variation about the neutral point, pH 7.00.

There was one outstanding feature of the reactions of duodenal specimens obtained after the feeding of the test meals and that was the wide range in fluctuation in the determinations of pH that frequently occurred in successive specimens. This has been noted by Mann and Bollman (3). It was not unusual for the reaction to vary from about 7.00 to about 3.00 in specimens withdrawn after an interval of a half hour. When such a low reading occurred after several high readings, it was not unusual for the pH of the next specimen to return to the previous high level. These results make it difficult to plot typical curves of the reactions of the specimens obtained after feeding. The most that can be said is that the determinations after a specific test meal resembled one another in the range of their variations.

The reactions of the specimens removed half an hour following a meal of 100 gm. of lean horse meat were usually acid whereas those an hour after feeding were invariably so. Specimens obtained one to four and a half hours after feeding were most acid and the reactions were usually between pH 5.00 and 3.00. After the four and a half hour period, the readings became less acid and, at the end of seven hours, were frequently neutral. However, it was not unusual for the readings to remain as acid as pH 5.00 seven hours after feeding meat.

The reactions of the specimens obtained after 200 gm. of lean horse meat varied but little from those obtained after 100 gm. of meat for the period of four and a half hours after feeding. From the four and a half to the seven-hour period the reactions after 200 gm. of meat usually remained as acid as before.

The specimens removed half an hour after the feeding of 100 gm. of corn syrup with 400 cc. of milk usually contained fine particles of curd. The acidity of the specimens generally varied between about pH 5.00 and 7.00 although occasionally more acid readings, as low as pH 4.00, occurred. The readings did not show such rapid fluctuations in acidity as those following a

meal of meat. At the end of seven hours, the reactions of the specimens were usually about neutral.

The majority of the specimens withdrawn after a meal of 100 gm. of lard with 100 gm. of cracker meal varied in acidity between the narrow range of pH 6.00 to 7.00. Two or three of the specimens within the seven-hour period usually showed a comparatively high acidity, which often reached pH 3.00. Generally, the following specimen would be between pH 6.00 and 7.00, although occasionally the acidity would fall more gradually.

*Results after making biliary fistulas.*—Three or four days after the operation for biliary fistula the second series of observations was begun. These observations were conducted under the identical conditions that prevailed during the first series. All the animals lost from 1 to 2 kg. during the first week after this second operation; but, after this initial loss, they usually maintained their weight. All of the animals readily ate the meat meals. Some of them showed a disinclination to eat the meal of milk and syrup, but all could be induced to do so. There was a tendency for them to refuse the meal of fat.

The reaction of specimens removed from dogs fasting from twenty-four to thirty-one hours after biliary fistulas had been made varied within the same range as specimens from normal dogs during the same period of fasting. The reactions of the specimens withdrawn twenty-four hours after feeding and just preceding the administration of the test meal were frequently slightly more acid than those obtained under normal conditions.

After the two meat meals, the reactions of the specimens compared very closely with the normal. The rise in acidity during the first four and a half hours and the subsequent return to about neutral was duplicated after 100 gm. of meat. After 200 gm. of meat, the acidity increased and remained about the same level as occurred in the experiments under normal conditions.

The loss of bile from the intestine did not cause any difference in the reactions of the specimens withdrawn after a meal of milk and syrup when compared with those obtained under normal conditions. In both series there was a variation in the specimens between pH 4.00 and 7.00.

The duodenal specimens following a meal of lard and crackers were generally more acid than normal specimens; whereas the reactions of the normal specimens varied between pH 6.00 and 7.00, these specimens usually ranged between pH 2.00 and 5.00.

## SUMMARY

Observations were made on the changes in pH of the duodenal content of dogs following various diets before and after draining the bile to the outside of the body. The results indicate that the loss of bile did not significantly alter the pH of the duodenal content under the conditions of these experiments.

## REFERENCES

1. Imms, P. R.: The reaction of the content of the isolated duodenum. *Am. Jour. Digest. Dis. and Nutr.* (In press).
2. Mann, F. C. and Bollman, J. L.: The reaction of the content of the gastro-intestinal tract. *J. A. M. A.*, 95:1722-1724 (Dec. 6) 1950.
3. Mann, F. C. and Bollman, J. L.: A method for making a satisfactory fistula at any level of the gastro-intestinal tract. *Ann. Surg.*, 93:794-797 (Mar.) 1931.
4. Rous, Peyton and McMaster, P. D.: A method for the permanent sterile drainage of intra-abdominal ducts, as applied to the common bile duct. *Jour. Exper. Med.*, 37:11-19 (Jan.) 1923.

# The Effect of Exclusion of the Pancreatic Secretion by Evulsion of the Pancreatic Ducts on the Reaction of the Duodenal Content\*

By

M. TISCHER HOERNER, M.D.\*\*  
ROCHESTER, MINNESOTA

THE secretion of the pancreas has usually been considered the most important of the three major secretions draining into the duodenum in maintaining the normal reaction of the duodenal content. It was the purpose of this investigation to attempt to quantify this important function of the pancreas.

The early literature on the subject can be briefly summarized by the statement that the results were quite variable, often contradictory, and possibly also unreliable. Uniformity of results was not obtained because of errors due to the disturbed function of the gastro-intestinal tract which were necessarily produced in the securing of specimens of duodenal content. The source of these errors was in the main corrected by the development of a satisfactory method of making a duodenal fistula.

## METHOD

Duodenal fistula, of the transposed loop of intestine type, was made in each animal used in this investigation. All operations were done with animals under ether anesthesia and using surgical technic. The routine procedure in making observations was as follows: The dogs were fasted for twenty-four hours before each test. After securing a specimen of duodenal content in the fasting state, the animal was fed one of the standard test meals. These test meals, four in number and representing a meal of protein, carbohydrate, and fat, were composed of the following foods: (1) 100 gm. of lean horse meat, (2) 200 gm. of lean horse meat, (3) 100 gm. of syrup mixed with 500 cc. of skimmed milk, and (4) 100 gm. of lard mixed with 100 gm. of cracker meal. Specimens of duodenal content were taken from the duodenal fistula at intervals of a half hour for eight hours or longer. For control observations the reaction of the duodenal content was determined in the same manner by omitting the test meals. The hydrogen ion concentration was determined by the quinhydrone gold electrode. Observations were repeated using the various diets until representative figures were secured for each animal.

As the next step in the investigation, the pancreatic ducts were evulsed. It is common knowledge that simple ligation of the pancreatic ducts does not obstruct the flow of pancreatic secretion, except for a very short period, as the ligature soon cuts through the duct establishing its patency. In order to obviate this chance for failure the ducts were evulsed by the following technic: Each duct was exposed at its point of entrance into the duodenal wall. A small hemostat

was placed securely on each duct and the duct was sectioned between the clamp and the duodenal wall. The clamp was then rotated, winding the duct around its lower end. In this manner all the ductal system was removed from the gland except the smaller tributaries. The procedure has been found to be perfectly safe as regards the life of the animal, and patency of the ductal system has never been established after the ducts were evulsed satisfactorily in this manner. The entire series of observations previously described were repeated on each animal after evulsion of the pancreatic ducts.

## RESULTS

It may not be entirely correct to consider that specimens withdrawn from a duodenal fistula are obtained under normal physiologic conditions, but since the animals remained in such excellent health and no change in gastro-intestinal function was demonstrable, such an assumption seemed justifiable in this research. It was found to be practically impossible to obtain a typical curve for the acidity of the duodenum during fasting and following the various types of diets used in the experiment, owing to continual variation of the reaction at all times. The wide range of fluctuation in successive specimens was remarkable. It was not unusual for samples taken at half-hour intervals to vary from a pH of 7.20 to 3.60. Thus the graphs made from these determinations consisted of a series of graduated spikes. The most that could be said of the results following a specific test meal was that they resembled each other in their range of variation.

*Normal reaction of the duodenal content.*—The reaction of the duodenal content during fasting was usually alkaline, varying from pH 7.00 to 7.81. However, if a sample was taken soon after the pylorus of the stomach had admitted a quantity of acid material, a pH as low as 3.31 was detected. Readings of 6.60 were not infrequent.

After a meal of 100 gm. of meat, the reaction of the duodenal content one-half hour later usually varied from pH 6.75 to 4.99, but determinations as low as 3.78 were observed. During the next one or two hours the fluctuations were marked, ranging from pH 6.40 to 3.50 with some readings as low as 1.93. Subsequently there was a gradual rise in the pH toward neutrality, but at any period during the next five hours a determination as low as 4.30 might be obtained. A value characteristic of the fasting state was never observed before six and a half hours, and at times not before ten to twelve hours, after the ingestion of food. Although a typical curve could not be obtained because of the irregular, marked fluctuations, it was noted that after the rapid decrease of the pH during the first two or

\*Portion of abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph. D. in Surgery.

\*\*Fellow in Surgery, The Mayo Foundation, Rochester, Minnesota. Submitted, May 12, 1935.

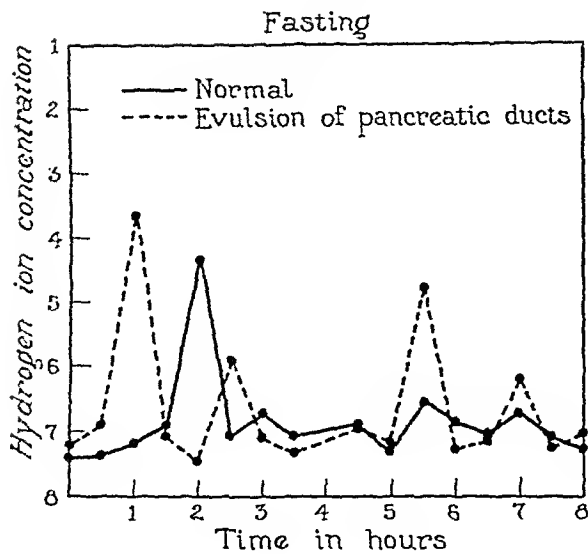


Fig. 1

three hours, there was a gradual tendency toward neutrality.

Following a meal of milk and syrup, the reaction of the duodenal content changed very little during the first half hour and was usually observed between pH 6.98 and 6.25. For the next two hours fluctuations as low as 4.26 were noted, but most of the values were not as low as those obtained with a meat diet. After the first two or three hours the return toward neutrality was rapid, but frequently, about six hours after the taking of the meal, there was a mild secondary decrease in the pH. Nevertheless, fasting readings were usually obtained from seven to eight hours after the ingestion of food.

A fat meal lowered the acidity of the duodenal content only to a slight extent, and the reaction remained fairly constant. The pH rarely decreased below 5.20 in the first two or three hours after taking food and thereafter usually varied from 6.80 to 6.25 with occasional readings of 5.80. However, at some period during the day a reading as low as 4.21 might be observed.

*Reaction of the duodenal content after evulsion of the pancreatic ducts.*—Following evulsion of the pancreatic ducts, the animals progressively lost weight although their appetite was excellent and they ate all the food offered them. When observations were not being made, the animals were fed the whole pancreas of calves three times a week with their regular rations. Their stools became exceedingly large, frequent, fatty, and rancid in odor. However, the animals remained very active and were apparently in excellent health except for the loss of weight.

During fasting, the range of variation in the reaction of the duodenal content was the same after evulsion of the pancreatic ducts as before, although wide fluctuations were more frequent than in the normal dog (Fig. 1).

Fig. 1. Variation in pH of the duodenal content of the fasting dog before and after evulsion of the pancreatic ducts.

Following a protein meal, the acidity of the duodenal content was increased more rapidly and was maintained for a longer period than before pancreatic secretion was eliminated. This result suggested the possibility that, owing to the absence of the pancreatic juice, the total buffer substances present were insufficient to maintain a normal reaction when a large quantity of highly acid chyme was poured into the duodenum. However, when the chyme decreased in amount, the quantity of available alkali was capable of gradually returning the reaction to normal (Fig. 2).

After a carbohydrate meal, the reaction of the duodenal content in a few instances closely approximated the average of the determinations obtained for the normal animal. However, in the majority of observations the increase in acidity came earlier after the ingestion of the meal, although it was not so soon or so great as occurred after taking meat, and was maintained for a longer period of time than in the normal dog (Fig. 3). The difference between the reaction of the duodenal content following a meat and a carbohydrate meal might have been the result of the fact that the carbohydrates were less stimulating than meat to acid secretion in the stomach, and thus the bile and succus entericus, although weaker buffering agents and not markedly stimulated by the carbohydrates, were able to maintain a more normal reaction.

As in the normal dog, a fat meal was followed by only a slight lowering of the acidity of the duodenal content. It is usually considered that fat is a depressant to gastric secretion. Thus it was reasonable to assume that, following a fat meal, the absence of the pancreatic juice had no effect on the reaction of the duodenal content because of the relatively low acidity of the chyme leaving the stomach.

Observations were continued for a period of two months following evulsion of the pancreatic ducts. All the animals were very active and apparently in the best of health at the end of this time except for loss in weight. Although the pancreas on examination at

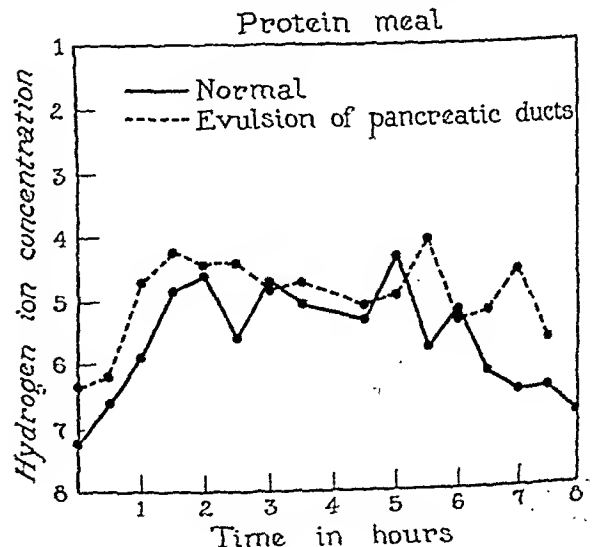


Fig. 2

Fig. 2. Variation in pH of the duodenal content of a dog after a protein meal before and after evulsion of the pancreatic ducts.



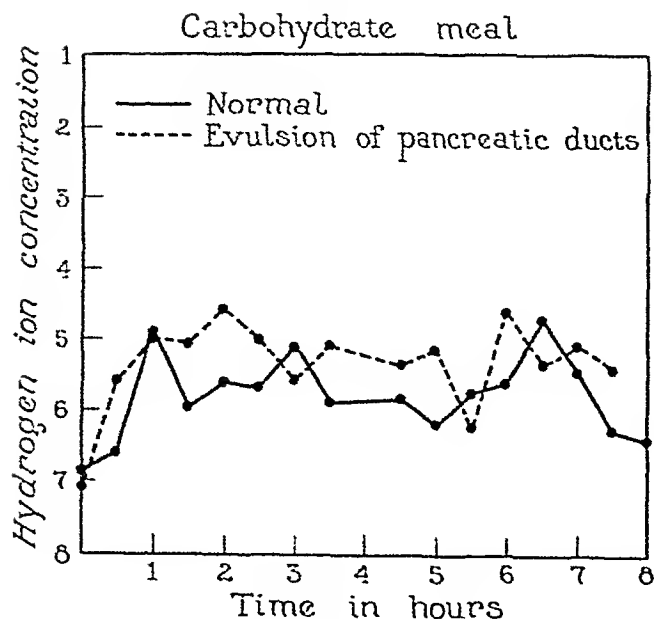


Fig. 3

necropsy was found to be merely a thin fibrous cord, no evidence of diabetes was discovered at any time during the investigation, which observation is in agreement with previous investigations.

#### COMMENT

Several sources of error which had to be eliminated were encountered in the course of the investigation. Owing to the innumerable conditions affecting the normal physiologic action of the gastro-intestinal tract, the training of the experimental animals was found to be an important factor. It was also noted that adherence to a regular routine was necessary in order to obtain consistent and reliable results. Although collection of the specimens was a simple process, care had to be taken that the catheter was not inserted too far. The position of the catheter in the duodenum was carefully checked by noting the length of the fistula at operation, marking the catheter, taking roentgenograms, and by fluoroscopic examination. As previously stated, it was necessary to evulse completely both pancreatic ducts and also to search carefully for an accessory duct that might have been overlooked. In one dog the minor duct broke before it was evulsed completely. On exploration three weeks later this duct was found to be patent and that portion of the pancreas which it drained was of normal size and appearance. The duct was again evulsed and the determinations repeated. Because of this observation in one case, the remainder of the dogs used in the investigation were explored and found to have small, fibrotic, atrophic pancreases.

Some of the results of this investigation necessitate additional comment. As might be expected, marked fluctuations in the acidity of the duodenal content of the normal animal were noted following administration of various types of test meal. On some days the observations were fairly consistent, but on others the fluctuations were remarkably varied. The same could be said of the results obtained following evulsion of the pancreatic ducts. These irregular determinations are explained by the fact that the reaction of the duodenal content is dependent on the saliva, food, gastric juice, bile, succus entericus, and pancreatic juice, and the rate at which the gastric content passes into the

Fig. 3. Variation in pH of the duodenal content of a dog following a carbohydrate meal before and after evulsion of the pancreatic ducts.

duodenum, all of which are exceedingly variable factors. Additional emphasis should be placed on the fact that the reaction of the duodenal content was always so varied that an average of the pH at any period was not a reliable index of the reaction at that time. Graphs made from the most characteristic figures obtained from each dog were the best means of illustration. In this investigation the absence of pancreatic juice produced a moderate change in the reaction of the duodenal content during fasting and following the protein and carbohydrate meals. In the first instance the change was characterized by more frequent low fluctuations, which were possibly due to the failure of the content of the fasting stomach to stimulate sufficient buffer substances because of the diminished amount immediately available. The variations in the duodenal content were more significant and consistent following meals of protein and carbohydrate, for the acidity was rapidly increased and was maintained at a higher level for a longer interval before returning toward neutral. Probably these results could not be accounted for by changes in the hydrogen ion concentration of the alkaline secretions alone, for undoubtedly dilution was an important factor. Thus the diminished amount of total buffers available could not cope with the large quantity of highly acid chyme. However, when the chyme decreased in amount and acidity, the reaction was gradually returned to normal. Perhaps such an assumption is controversial, but the fact remains that the bile and succus entericus, while usually of minor importance in the reaction of the duodenum, apparently are capable of maintaining the reaction of the duodenal content almost normal in the absence of pancreatic secretion.

#### SUMMARY

Determinations of the reaction of the duodenal content of dogs were made before and after evulsion of the pancreatic ducts in the fasting state and after the ingestion of various standard test meals. The reaction of the duodenal content in the fasting state was usually alkaline, ranging from pH 7.00 to 7.81. After a meat meal, the pH varied between 6.40 and 3.50. Following a carbohydrate meal, the reaction ranged from 6.75 to 4.26. The fat meal caused fluctuations from 6.80 to 5.20. Thus the acidity of the duodenum after meals appeared to depend largely on the rate and amount of acid formation in the stomach.

Following evulsion of the pancreatic ducts, the reaction of the duodenal content during fasting possessed the same range of variation as when the pancreatic secretion was present, but determinations on the acid side of neutrality were obtained more frequently. Both protein and carbohydrate test meals caused the duodenal content to become acid in reaction more rapidly, and the reaction was maintained for a longer period before returning toward neutrality after loss of the pancreatic secretion than in the normal state. With the pancreatic juice absent, the total buffer secretions in the duodenum were diminished, but the remaining secretions, bile and succus entericus, were capable of maintaining a normal reaction of the duodenal content except when a gastric content of high acidity entered the duodenum.

# The Effect of Exclusion of the Pancreatic Secretion by a Pancreatic Fistula on the Reaction of the Gastric, Duodenal and Jejunal Contents\*

By

M. TISCHER HOERNER, M.D.  
ROCHESTER, MINNESOTA

THE effect of the loss of the secretion of a gland is not necessarily the same as the effect of preventing the gland from secreting. The secretion of the pancreas is a pertinent example. The loss of pancreatic secretion produces a rapidly fatal result unless appropriate treatment is instituted. On the other hand, evulsion of the pancreatic ducts, preventing the production of pancreatic secretion, produces no untoward effects except those associated with the resulting decrease in intestinal digestion. The results of eliminating the pancreatic juice, by preventing the pancreas from secreting, on the reaction of the duodenal content were presented in the previous paper. It was the purpose of this investigation to determine what changes in the reaction of the content of the upper portion of the gastro-intestinal tract occur when the pancreatic secretion is eliminated by draining it to the outside of the body.

## METHOD

Gastric, duodenal, and jejunal fistulas, as well as combinations of these fistulas, employing the transposed loop of intestine method, were made (3) and utilized in obtaining specimens of the content of the upper portion of the gastro-intestinal tract at half-hour intervals for an eight-hour period. The hydrogen ion concentration of this material was determined at once with quinhydrone gold electrode. Samples of the content of the various portions of the gastro-intestinal tract were collected during fasting and following the administration of the standard protein, carbohydrate, and fat test meals until representative figures were secured for each animal. Having obtained the necessary preliminary data, pancreatic fistulas were made using a technic similar to that of Elman and McCaughan. It was found advantageous to feed the dogs 50 gm. of meat about three hours before the operation. Thus the major pancreatic duct was more easily cannulated and secretion immediately began to flow through the tube, preventing the formation of blood clots that might lead to obstruction of the cannula. The same series of tests were then performed and similar observations instituted the day following operation. The animals were given daily 300 to 600 cc. of physiologic saline solution intravenously, depending on the size of the animal and the amount of pancreatic juice secreted during the preceding twenty-four hours. This procedure, so necessary for the maintenance of life, replaced both the fluid and salt which had been lost from the pancreatic fistula and by vomiting. The operations

were performed with animals under ether anesthesia and employing sterile technic.

## RESULTS

Elman and McCaughan reported that death invariably resulted in from five to eight days when the entire external pancreatic secretion of dogs was excluded from the intestine by drainage to the outside of the body. However, the later work of McCaughan revealed that, if the whole pancreatic juice was returned to the dog by mouth or large quantities of physiologic saline solution were injected intravenously daily, no untoward effects were noted. The results of these experiments substantiated the findings of the foregoing authors. Although the dogs in this group ate fairly well, they gradually lost weight, and practically all of them developed a tendency to vomit occasionally. As in the case of evulsion of the pancreatic ducts, the stools became large, fatty, and rancid in odor.

*Effect on the reaction of the gastric content.*—The reaction of the gastric content (after establishing the pancreatic fistula) during fasting and following the ingestion of the standard test meals was always within normal limits.

*Effect on the reaction of the duodenal content.*—Specimens of the duodenal content during fasting usually had a pH between 7.00 and 7.78, but variations from 6.80 to 5.41 were sometimes observed. Nevertheless, when samples were taken at half-hour intervals for an eight-hour period, an occasional acidity as low as 3.07 was detected among these alkaline and slightly acid readings. A comparison between these findings and those from the normal dog revealed that, following the production of a pancreatic fistula, determinations below pH 7.00 were more frequently obtained and the levels reached were somewhat lower in the majority of cases.

The reaction of the duodenal content the first half-hour after a meat meal was found to be between pH 5.95 and 4.12, but during the next two or three hours it ranged from 4.50 to 2.50. Although there was then a tendency to return toward neutral, the majority of the subsequent determinations remained between 5.00 and 3.98. When the pancreatic secretion was eliminated by draining to the outside of the body, the results were similar to those obtained when the gland was prevented from secreting (Fig. 1).

One-half hour after the administration of a test meal composed of milk, syrup, and water, the pH of the duodenal content ranged from 6.60 to 5.88. A further increase in the acidity, fluctuating between 5.95 and 4.20, was detected during the following two or three hours, but a specimen with a pH as low as 3.69 was occasionally collected. Thereafter, although

\*Portion of abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph. D. in Surgery.  
Fellow in Surgery, The Mayo Foundation.  
Submitted May 12, 1935.

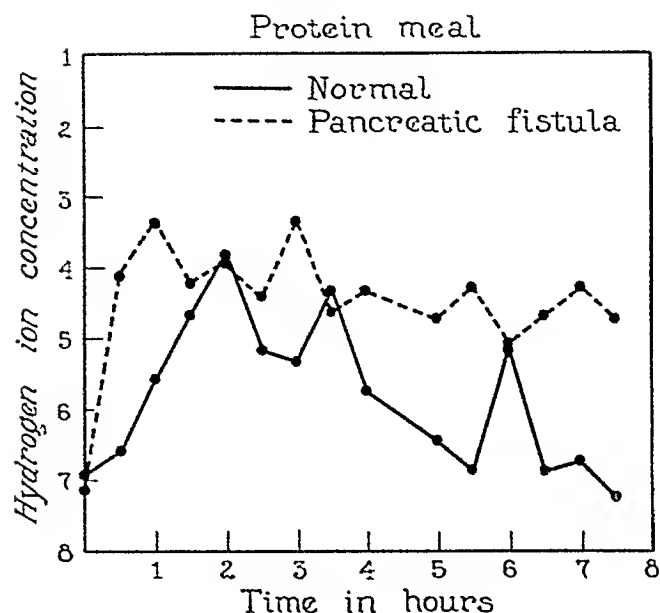


Fig. 1

the reaction usually returned to a higher level, varying between 6.50 and 5.06, a reading of 4.21 was sometimes obtained, which not infrequently was the lowest determination occurring throughout the day (Fig. 2).

After a fat meal, no deviation from normal could be detected in the pH of the duodenal content following the production of a pancreatic fistula.

*Effect on the jejunal content.*—By the time the gastric content admitted into the duodenum had reached the jejunum, its reaction was neutral or was slightly alkaline. The loss of pancreatic secretion did not appear to injure the mechanism accomplishing this change except when a protein test meal had been administered.

The ingestion of a protein meal was followed by a gradual decrease in the pH of the jejunal content until a level of 5.00 was reached about two and a half hours after the ingestion of food. Subsequent determinations closely approximated those of the normal dog, but acid readings as low as 5.78 were more frequently obtained. Thus the absence of the pancreatic juice did have a slight but appreciable effect on the reaction of the intestinal content below the duodenum with this diet.

*Comparison of results obtained with pancreatic fistulas and evulsion of pancreatic ducts.*—By careful selection of observations from each group the change in the reaction of the duodenal content could be made to appear more marked following either evulsion of the ducts or establishment of a pancreatic fistula. A reliable opinion concerning any real difference could only be formed when both series of dogs were considered in their entirety. It was then discovered that a few more acid determinations were obtained with a pancreatic fistula following protein and carbohydrate diets than after evulsion of the pancreatic ducts. However, the distinction was so slight that it should not be emphasized.

Fig. 1. Variation in the pH of the duodenal content following a protein meal before and after the establishment of a pancreatic fistula.

### COMMENT

With the aid of daily intravenous injections of physiologic saline solution the dogs remained active and in apparently good health for many days although they continued to lose weight. One animal was kept in excellent condition for thirty-four days, but there was some evidence of leakage of the pancreatic juice into the intestine about the twentieth postoperative day, and this was verified on postmortem examination. Two dogs died after continuous secretion for seven and twenty-five days, respectively, and necropsy revealed no cause of death other than the pancreatic fistulas. The findings at necropsy of two other animals, both lost on the tenth day, revealed acute perforated peptic ulcers.

It was essential to maintain a continuous flow of secretion after establishing a pancreatic fistula. The development of leakage or infection had to be detected immediately and the dogs eliminated from the series. Owing to the extreme facility with which the pancreatic juice became infected in spite of a strict aseptic technic, the remainder of the dogs, although in fairly good condition and excreting pancreatic juice freely, were sacrificed from twelve to twenty-four days postoperatively because of the presence of bacteria in the pancreatic secretion. At times the material collected from the fistula was perfectly clear and was of normal appearance, and the existence of an early infection could be detected only by special technic.

### SUMMARY

Specimens were obtained of gastric, duodenal and jejunal contents under normal physiologic conditions and their reactions were determined in the fasting state and after various test meals, before and after draining the pancreatic secretion to the outside of the body. The production of a pancreatic fistula caused no change in the reaction of the gastric content during fasting or after the various types of test meal used in the research. However, differences in the reaction

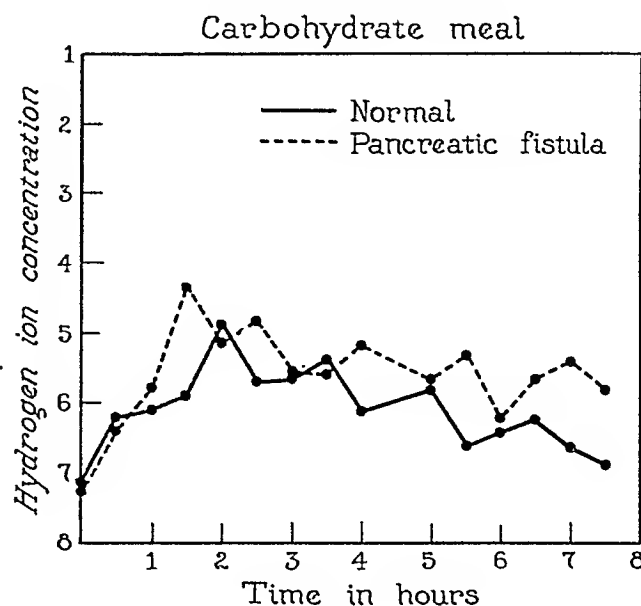


Fig. 2

Fig. 2. Variation in the pH of the duodenal content following a carbohydrate meal before and after the establishment of a pancreatic fistula.

of the duodenal content were observed after establishing a pancreatic fistula. Although the range of variation during fasting was quite within normal limits in the two conditions, low determinations were more frequently obtained for the animal with a pancreatic fistula. Protein and carbohydrate meals caused a more rapid decrease of the pH, and the reaction was usually maintained at a decreased level for a longer period before returning toward neutrality than was found be-

fore elimination of the pancreatic secretion. These same changes were also observed to a lesser degree with the jejunal content, but only after a protein diet. A comparison of the results following the production of a pancreatic fistula and evulsion of the pancreatic ducts revealed a few more acid determinations in the former after protein and carbohydrate diets. The distinction, however, was slight and should not be emphasized.

### REFERENCES

1. Elman, Robert and McCaughan, J. M.: On the collection of the entire external secretion of the pancreas under sterile conditions and the fatal effect of total loss of pancreatic juice. *Jour. Exper. Med.*, 45:561-570, March, 1927.
2. McCaughan, J. M.: Experimental studies of the external secretion of the pancreas with special reference to the effect of its complete loss by permanent pancreatic fistula. I. The coincident changes in the chemistry of the blood. II. The mechanism of death. *Am. Jour. Physiol.*, 97:459-466, June, 1931.
3. Mann, F. C., and Hollman, J. L.: A method for making a satisfactory fistula at any level of the gastro-intestinal tract. *Ann. Surg.*, 93:791-797, March, 1931.

## The Buffer Capacity of the Pancreatic Juice\*

By

M. TISCHER HOERNER, M.D.\*\*

ROCHESTER, MINNESOTA

WHILE ascertaining the reaction of the intestinal content at various levels of the intestinal tract following elimination of the pancreatic secretion from the duodenum by means of a pancreatic fistula, it seemed desirable to determine whether the results obtained in previous studies could mainly be due to the absence of the secretion from the pancreas.

Bayliss and Starling stated that the alkalinity of pancreatic juice gradually fell as secretion continued. Anrep, Lush, and Palmer believed this was partly due to removal of available alkalis from the blood supply and partly to the slightly acid solutions of secretin which were used to stimulate the pancreas. Johnston and Ball noted that the pH of pancreatic juice varied from 7.16 to 8.04 during constant drainage of the secretion, and that a decrease of chloride ions was associated with an increase of bicarbonate. Ball (2, 3), also reported that the more rapidly the juice was secreted the higher its pH value, and that the bound carbon dioxide concentration of chloride and bicarbonate varied inversely. Gamble and McIver discovered that this decrease in chloride in the pancreatic juice was associated with a diminution in the chloride concentration of the blood.

Mellanby stated that secretin controlled only the alkaline fluid of the pancreatic juice, whereas the enzymes were produced by a nervous mechanism. This was in accordance with the views of Zucker, Newburger, and Berg. Dubois and Polonovski also supported this theory, for they observed that the reaction of the pancreatic secretion following the injection of secretin into five dogs varied between pH 8.4 and 8.6, and that following the injection of pilocarpine it varied between 7.8 and 8.2. Popow and Kudrjawzew found

the hydrogen ion concentration of pancreatic secretion to be inversely proportional to that of fluid introduced into the duodenum to stimulate the secretion of the juice. The work of Carnot and Gruzewska appeared to substantiate this observation, as they noted that the pancreatic secretion had a pH of 8.72 and, after injection of histamine, a pH of 8.90. In addition, Czubalski reported that the pH of the pancreatic secretion fluctuated between 7.06 and 8.64, and that the secretion was more alkaline following a protein meal (pH 8.23 to 8.64) than after the ingestion of milk (pH 7.06 to 8.45). He reasoned that since milk did not produce so high an acidity in the stomach, pancreatic secretion which had a reaction nearer neutral was produced. However, Jones felt that there was a compensatory reaction between the bile and pancreatic juice so that when the buffer action of one decreased the other tended to increase.

Under the conditions of their investigation, Elman and McCaughan found the buffering capacity of the pancreatic secretion to be very great, for 1 c.e. of the secretion would neutralize an equal amount of tenth-normal hydrochloric acid, and thus they considered it an important factor in the neutralization of acid chyme.

### METHOD

In this experiment, 1 c.e. of the secretion secured from the pancreatic fistula was titrated with 1 c.c. of tenth-normal hydrochloric acid, a drop at a time, and the change in pH with each minute addition was determined. Samples of pancreatic juice were collected at half-hour intervals during fasting and after the ingestion of the various standard test meals and the fluctuation in the buffering capacity during the eight-hour period of observation was determined.

### RESULTS

The pancreatic secretion was usually thin, watery, opalescent, and tasteless when flowing freely, but was somewhat more viscid and ropy in character after

\*Portion of abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph. D. in Surgery.

\*\*Fellow in Surgery, The Mayo Foundation, Rochester, Minnesota. Submitted, May 12, 1935.

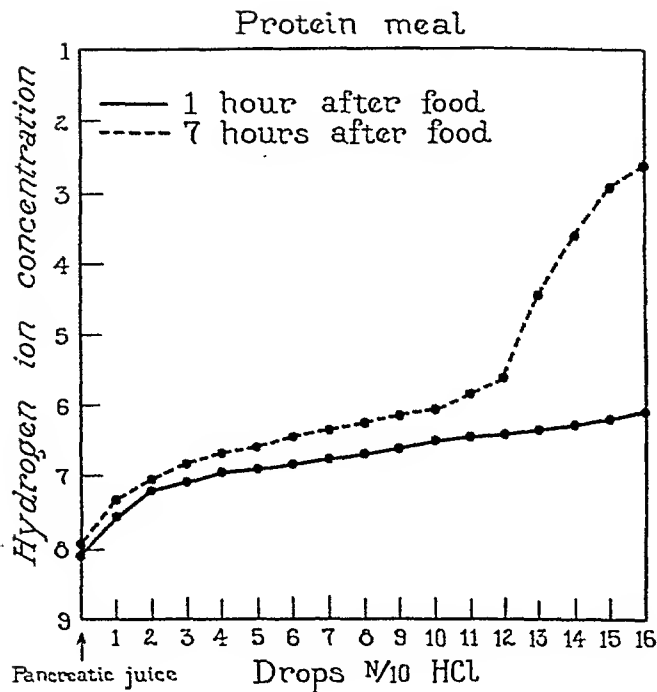


Fig. 1

prolonged fasting. Protein seemed to stimulate a more copious secretion than any of the other test meals used. During fasting the amount collected was greatly diminished, but even in the fasting state the secretion was continuous, provided there was no leakage or infection. Infection of the fistulous tract did not immediately change the appearance of the pancreatic juice, but after the infection had persisted for a short time the secretion became turbid and contained small flakes, composed of bacteria, leukocytes, and bits of tissue. The amount of secretion collected was exceedingly variable, depending apparently on the size of the animal and the kind and quantity of the food given. After the first day the amount of secretion obtained might vary, but on an average the twenty-four hour total fluctuated between 150 and 400 cc. of pancreatic juice.

There was a rather rapid increase in the buffering capacity of the secretion half an hour after the administration of a protein meal when compared with that obtained during fasting. The buffering capacity increased still further during the next two or three hours, the pH fluctuating between 6.02 and 5.81 after the addition of 1 c.c. of the acid. However, the material collected subsequently was not so capable a buffer, for the pH was rapidly lowered to levels between 3.22 and 2.65. These results suggested that the meat meal immediately stimulated the production of a large amount of pancreatic juice possessing considerable buffering power, and that later, after acidity in the duodenum had decreased, there was a corresponding diminution in the neutralizing substances present in the pancreatic secretion (Fig. 1).

The buffering power of the pancreatic juice after a carbohydrate meal was not so great half an hour after

Fig. 1. Titration curve (buffer value) of pancreatic juice at the end of one and seven hours following a protein meal.

eating as that developed following a protein diet. However, the neutralizing properties gradually increased until they reached their maximal value about one and a half hours after the ingestion of food. This efficiency was not maintained, as with a meat meal, and was gradually lost during subsequent observations. These figures revealed that it took a longer time to incite the production of buffering substances in the pancreatic juice and that they diminished sooner after developing their maximal potency with the carbohydrate meal than with a protein meal (Fig. 2).

The assimilation of a fat diet was followed by only a slight increase in the amount of the buffering substances present in the pancreatic juice a half hour after ingestion, but, by the end of one and a half hours, their value closely approximated that obtained with the other foods. However, owing to the fact that the acidity developed in the duodenum was not so marked as in the other instances, it was quite natural that the neutralizing power of the secretion should diminish rapidly during succeeding observations.

During fasting, although there was no stimulation or buffer substances in the pancreatic juice by food, the secretion still possessed some buffering power. Occasionally the characteristic buffering effect after the addition of the first few drops of hydrochloric acid could be detected, but in the majority of instances the pH was rapidly lowered to a rather uniform level.

#### COMMENT

The graphs representing the pH of the pancreatic juice after the various types of diets possessed several characteristics in common. When hydrochloric acid was first added to the secretion, the pH dropped rapidly, just as when water is added to acid. After a few drops, however, the action of the buffering substance soon became apparent, for the curves remained fairly

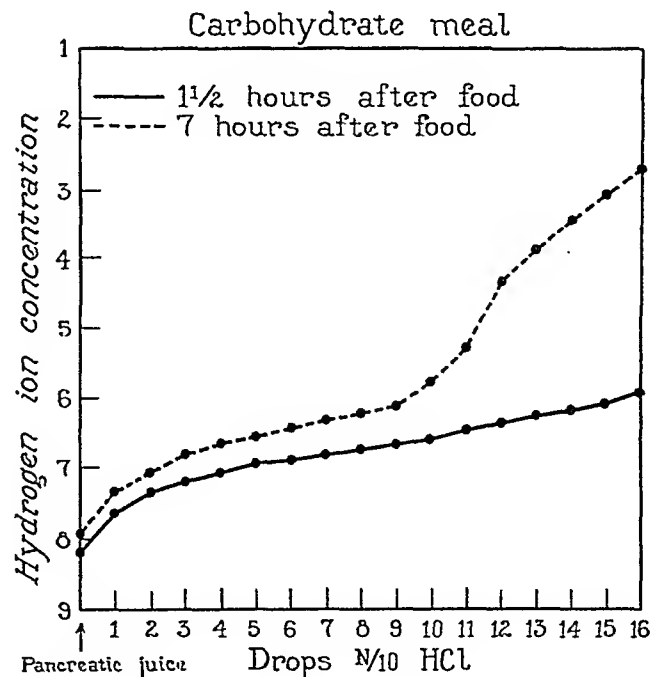


Fig. 2

Fig. 2. Titration curve (buffer value) of pancreatic juice at the end of one and seven hours following a carbohydrate meal.

level in spite of the increasing amount of acid present. When the neutralizing power of the pancreatic juice was finally exhausted, the pH rapidly proceeded to rather low levels, again quite similar to the result obtained by the addition of water to acid. The buffering value developed following each test meal was approximately the same, but the capacity of the secretion in this respect was lost more rapidly with the carbohydrate and fat meals than with the protein meal, probably as a result of the difference in the acid level produced in the duodenum by these various diets. Thus the results obtained during this experiment appeared to substantiate Elman's and McCaughan's findings, for the pancreatic juice was always alkaline even after continuous secretion for thirty-four days and when infection and leakage were known to exist. In addition the buffering value of the secretion was exceedingly high following the ingestion of all types of test meals.

## SUMMARY

An investigation was conducted on the properties of the pancreatic juice collected from pancreatic fistulas every half hour during fasting and after the ingestion of protein, carbohydrate, and fat test meals. A continuous secretion of pancreatic juice was noted at all times, provided there was no infection or leakage present. Protein diets stimulated a greater flow of secretion than any of the other test meals used. The amount of secretion depended largely on the size of the animal and the kind and quantity of food ingested. The buffering capacity of the pancreatic juice reached its maximum one to three hours after the ingestion of food and gradually diminished as the acidity in the duodenum decreased. The secretion was always alkaline and even possessed slight buffering power during fasting. When the buffering capacity was highest, 1 c.c. of pancreatic juice was capable of practically neutralizing an equal quantity of tenth-normal hydrochloric acid.

## REFERENCES

1. Anrep, G. V., Lush, Joan L. and Palmer, M. Grace: Observations on pancreatic secretion. *Jour. Physiol.*, 50:134-412 (Mar. 31) 1925.
2. Ball, E. G.: The composition of pancreatic juice and blood serum as influenced by the injection of acid and base. *Jour. Biol. Chem.*, 86:133-415 (Apr.) 1930.
3. Ball, E. G.: The composition of pancreatic juice and blood serum as influenced by the injection of inorganic salts. *Jour. Biol. Chem.*, 86:449-462 (Apr.) 1930.
4. Bayliss, W. M., and Starling, E. H.: On the uniformity of the pancreatic mechanism in vertebrates. *Jour. Physiol.*, 29:174-180 (Mar. 16) 1903.
5. Carnot, P., and Gruzewski, Z.: Variations de concentration ionique de la bile et du suc pancréatique pendant la sécrétion acide du suc gastrique. *Compt.-rend. Soc. de Biol.*, 93:240-242 (July 3) 1925.
6. Czubalski, P.: L'influence de l'alimentation sur la concentration en ions hydrogène (pH) du suc pancréatique. *Compt.-rend. Soc. de Biol.*, 97:954-955 (Oct. 13) 1927.
7. Dubois, C., and Polonovski, Michel: Sur la concentration en ions hydrogène du suc pancréatique. *Compt.-rend. Soc. de Biol.*, 93:632-633 (Aug. 14) 1925.
8. Elman, R., and McCaughan, J. M.: On the collection of entire external secretion of pancreas under sterile conditions and total effect of total loss of pancreatic juice. *Jour. Exper. Med.*, 45:561-570 (Mar.) 1927.
9. Gamble, J. L., and Melver, M. A.: Acid-base composition of pancreatic juice and bile. *Jour. Exper. Med.*, 48:849-857 (Dec.) 1928.
10. Johnston, C. G., and Ball, E. G.: Variations in inorganic constituents of the pancreatic juice during constant drainage of the pancreatic ducts. *Jour. Biol. Chem.*, 86:643-653 (Apr.) 1930.
11. Jones, K. K.: Comparison of buffer value of bile and pancreatic juice secreted simultaneously. *Proc. Soc. Exper. Biol. and Med.*, 28:567-568 (Mar.) 1931.
12. Mellanby, J.: The secretion of pancreatic juice. *Jour. Physiol.*, 61:419-435 (June 22) 1926.
13. Popow, N. A., and Kudrjawzew, A. A.: Zur Lehre der Anpassungsfähigkeit der Arbeit der Bauchspeicheldrüse und die Eigenschaften des Reizmittels. Der Einfluss des Gehalts an Säure in der in das Duodenum eingeführten Flüssigkeit auf pH des Bauchspeicheldrüsensaftes. *Arch. f. d. ges. Physiol.*, 224:56-68, 1930.
14. Zucker, T. F., Newburger, P. G., and Hers, B. N.: Chemical differentiation of nervous and hormonal pancreatic secretion. *Proc. Soc. Exper. Biol. and Med.*, 30:166-167 (Nov.) 1932.

# Peptic Ulcer Following Loss of Pancreatic Secretion Through a Fistula: An Experimental Study

By

M. TISCHER HOERNER, M.D.  
ROCHESTER, MINNESOTA

WHILE studying the effect of exclusion of the pancreatic secretion on the content of the upper portion of the gastro-intestinal tract, it was noted that peptic ulcer developed in some of the animals in which the pancreatic secretion was excluded from the duodenum by a pancreatic fistula, whereas in no instance was an ulcer found in those animals in which the secretion of the pancreas was excluded by evulsion of the pancreatic ducts.

These observations are in accord with those noted by previous investigators. Many investigations have been made in which for one purpose or another the pancreatic ducts have been ligated or evulsed. In very

few instances have peptic ulcers been noted following this procedure even when the animals lived for many months after exclusion of the pancreatic secretion. It should also be noted that peptic ulcer is rarely found in depancreatized animals. On the other hand, as the investigations of Elman and Hartmann, Dragstedt, Montgomery and Ellis proved, loss of pancreatic secretion through a fistula is followed by the development of peptic ulcers in the duodenum in a very high percentage of experiments.

It is evident, in so far as the development of duodenal ulcer is concerned, that the loss of pancreatic secretion from the body causes some change which does not occur when the pancreas is prevented from secreting. On the other hand, as the results of my



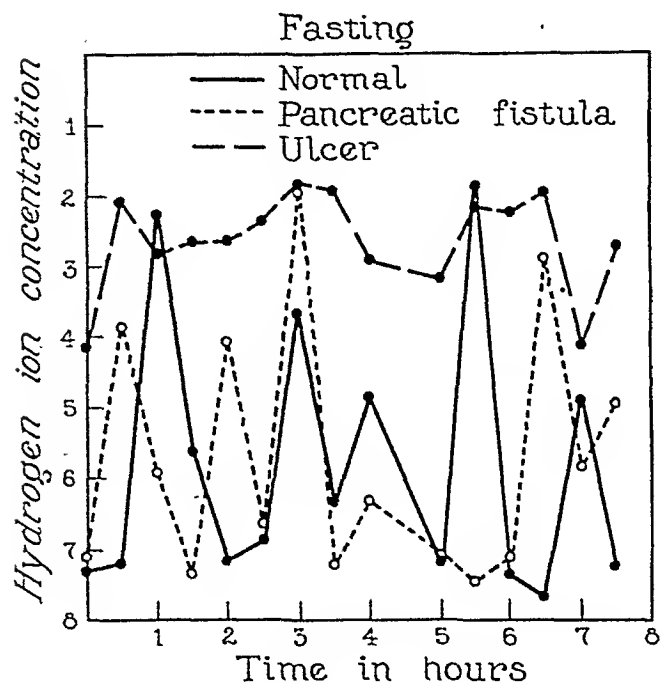


Fig. 1

previous investigations show, exclusion of the pancreatic secretion from the duodenum by a pancreatic fistula and by evulsion of the pancreatic ducts causes almost identical changes in the reaction of the duodenal content. With these facts in mind it seemed desirable to determine whether there was any significant change in the reaction of the content of the upper portion of the gastro-intestinal tract associated with the development of the ulcer that occurs after draining the pancreatic secretion to the outside of the body.

#### METHOD

Gastric, duodenal, and jejunal fistulas, as well as combinations of such fistulas, were made according to the transposed loop of intestine method (3) and were utilized in obtaining specimens from the upper portion of the gastro-intestinal tract at half-hour intervals during an eight-hour period. The hydrogen ion concentration of such specimens was determined at once by the quinhydrone gold electrode and potentiometer. Samples were collected during fasting and following the administration of protein, carbohydrate, and fat test meals until representative figures were secured at the various levels for each dog used in the experiment. Pancreatic fistulas were then made according to the technic of Elman and McCaughan and the forementioned tests were repeated. The dogs were given 300 to 600 c.c. of physiologic saline solution intravenously every day, depending on the size of the animal and the amount of pancreatic juice secreted during the preceding twenty-four hours.

It was impossible to determine positively before necropsy whether an ulcer had developed. It was also impossible to know when an ulcer was in the process of formation. These difficulties were at least partially overcome by making repeated tests until the animal died or was sacrificed because of infection or because

Fig. 1. Variations in the pH of the gastric content in the fasting state, before and after establishing a pancreatic fistula and during or after the development of a duodenal ulcer.

leakage of the pancreatic secretion had occurred. The presence or absence of duodenal ulcer was determined at necropsy. The data were then assembled in two groups: those secured from the animals in which ulcer was present and those secured from the animals in which no lesion in the duodenum was present.

#### RESULTS

After the production of pancreatic fistulas in these animals no change in the reaction of the gastric content was noted during fasting or following the ingestion of protein, carbohydrate, or fat test meals. In the duodenal content, however, although the variation in the reaction during fasting was within normal limits, a low pH was more frequently obtained. Protein and carbohydrate test meals were followed by a more rapid lowering of the pH, and this low level was maintained for a longer period than in the normal dog. Similar changes were sometimes observed in the jejunum, but only after a protein diet.

Elman and Hartmann reported the development of duodenal ulcers in all of their dogs in which they had made pancreatic fistulas. In this investigation ulcers were found in only 42 per cent of the animals, but this high incidence appears to be of considerable significance. A comparison of the observations made on animals in which ulcer developed and on those in which the lesion did not develop showed that the development of ulcer was apparently accompanied by a very definite change in the reaction of the content at all levels of the gastro-intestinal tract that were examined. These changes began from six to fifteen days after making the pancreatic fistula. The reactions of the gastric, duodenal, and jejunal content of animals with peptic ulcers can be summarized as follows:

**Stomach.** As much as 15 c.c. of grayish mucoid material could easily be withdrawn from the fasting stomach at the time the ulcer appeared to be develop-

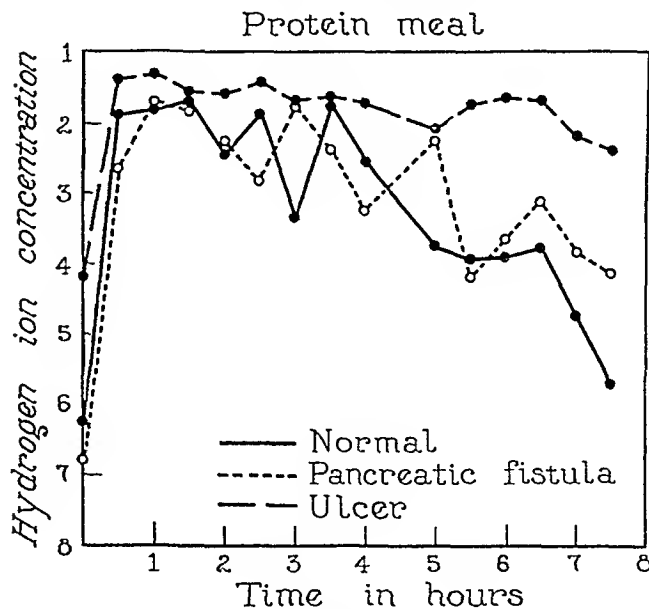


Fig. 2

Fig. 2. Variations in the pH of the gastric content after a protein meal, before and after establishing a pancreatic fistula and during or after the development of a duodenal ulcer.

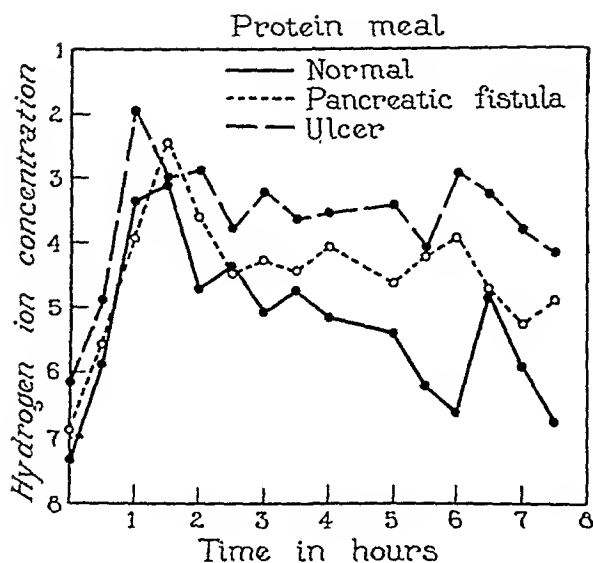


Fig. 3

ing. These samples possessed an exceedingly low pH, fluctuating between 1.50 and 3.00. The gastric acidity had never been found to be maintained at such a level during fasting before the development of the ulcer or in animals in which ulcer was not found (Fig. 1).

The reaction of the gastric content after a protein meal was always quite high, so that the secondary increase in acidity was not so apparent as in the fasting state. It was quite evident, however, that a pH which often ranged between 1.50 and 2.00 was definitely lower than that found in previous observations (Fig. 2).

**Duodenum.** When a dog had a peptic ulcer, the pH of the duodenal content following a protein meal varied from 3.00 to 4.00, which was a somewhat lower level than was observed in animals in which ulcer was not present (Fig. 3). Under similar circumstances a definite increase in the duodenal acidity was also noted during fasting and after carbohydrate and fat test meals.

**Jejunum.** The reaction of the jejunal content, which is usually quite constant, showed changes in animals that had an ulcer (Figs. 4 and 5).

In the fasting state the pH of the content of the jejunum ranged from 4.50 to 6.00, with occasional lower readings in animals in which ulcer was found, instead of a pH of 7.00 or higher as is usually observed. At times as much as 7 c.c. of this gray or yellow-brown material could be collected, which was an unusual amount at this level of the intestine during fasting.

After a meat meal the jejunal content of these animals had a pH which varied between 3.50 and 5.00. Thus the increased amount of highly acid material from the stomach could not be neutralized as formerly, or its passage down the intestine was more rapid.

Carbohydrate and fat meals were followed by similar changes in the reaction of the jejunum, but they were not so marked as those observed after a protein diet.

Fig. 4. Variations in the pH of the jejunal content in the fasting state, before and after establishing a pancreatic fistula and during or after the development of a duodenal ulcer.

Fig. 3. Variations in the pH of the duodenal content after a protein meal, before and after establishing a pancreatic fistula and during or after the development of a duodenal ulcer.

### COMMENT

It is definitely shown by these investigations that the effect of the loss of secretion of the pancreas is not necessarily the same as the effect of preventing the gland from secreting. When pancreatic fistulas were established, thus eliminating the pancreatic secretion from both the duodenum and the body, duodenal ulcers developed in 42 per cent of the animals. However, when the pancreatic ducts were evulsed, thus likewise eliminating the pancreatic juice from the duodenum but without loss of the secretion, ulcer did not occur. It is difficult to explain why drainage of the pancreatic juice to the outside of the body was associated with the formation of peptic ulcers, and why elimination of the secretion from the duodenum by evulsion of the pancreatic ducts did not have a similar effect, because it is quite obvious that the slight difference in the reaction of the duodenal content resulting from the two procedures was not the significant factor involved.

In this regard it should be pointed out that, when the pancreatic juice was drained to the outside of the body, the fluid and sodium chloride were replaced in the form of daily intravenous injections of physiologic saline solution, but, that the other salts were entirely lost along with the secretion. On the other hand if the pancreatic ducts were evulsed, the fluid and basic salts were not lost but were retained in the body. This might account for the better condition and longer life of the animals following the latter procedure. Loss of certain constituents in the pancreatic secretion may be an important factor in the formation of the lesions. Nevertheless, whatever the correct explanation may be, it is safe to assume that the mere absence of the pancreatic juice from the duodenum was not the main element involved in the development of peptic ulcer.

The unavoidable variable conditions under which the observations were made make it hazardous to draw

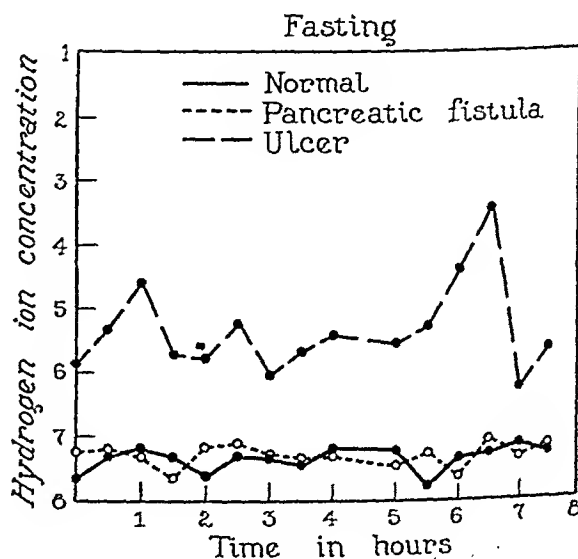


Fig. 4

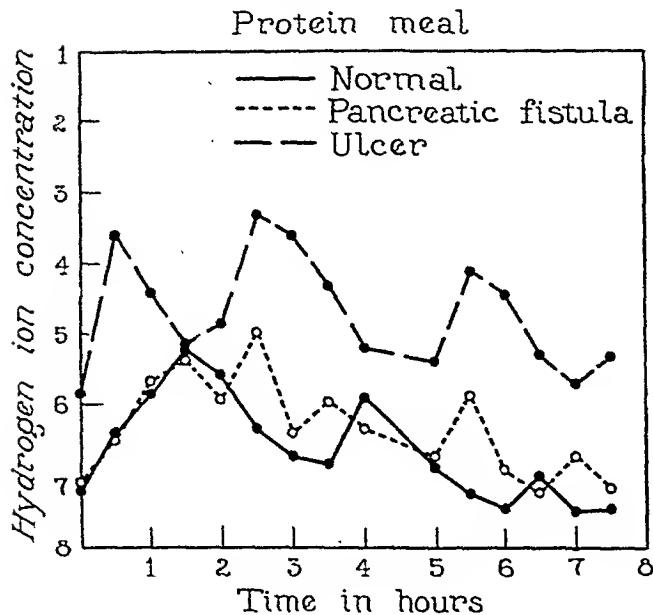


Fig. 5

definite conclusions. The results, however, appear to indicate that there was an increase in both the amount and acidity of the content of the upper portion of the gastro-intestinal tract in the animals in which ulcer was found. Whether these changes occurred before or after the development of the lesions could not be ascertained. Likewise it was impossible to determine whether or not these changes were dependent on some concomitant factor such as hemorrhage from the ul-

Fig. 5. Variations in the pH of the jejunal content following a protein meal, before and after establishing a pancreatic fistula and during or after the development of a duodenal ulcer.

erated surface. Often a small amount of blood in the stomach or duodenum will produce a change in the reaction of the content of the upper portion of the gastro-intestinal tract. It can be definitely stated, however, that loss of the function of the pancreatic secretion, in regard to neutralizing, buffering, and diluting the gastric chyme, is not the only factor responsible for the lesions.

### SUMMARY

Specimens of the content of the upper part of the gastro-intestinal tract of dogs were collected during fasting and after the administration of various diets. Following the production of a pancreatic fistula in these animals, no change in the pH of the gastric content was detected, but the duodenal pH during fasting was more variable and after ingestion of protein and carbohydrate meals a lower value was reached and was maintained for longer periods than normally. The latter observation was sometimes noted in the jejunum after a protein diet. Peptic ulcer occurred in 42 per cent of the animals in which a pancreatic fistula was made. There appeared to be an increase in the amount of material obtained from the stomach, duodenum, and jejunum during fasting and after different test meals, as well as an increase in the acidity of the material, in the animals in which ulcer was found at necropsy.

### REFERENCES

1. Dragstedt, L. R.; Montgomery, M. L., and Ellis, J. C.: A new type of pancreatic fistula. *Proc. Soc. Exper. Biol. and Med.*, 28:109-110, 1930.
2. Elman, Robert and Hartmann, A. F.: Spontaneous peptic ulcers of the duodenum after continued loss of total pancreatic juice. *Arch. Surg.*
3. Elman, Robert and McCaughn, J. M.: On the collection of the entire external secretion of the pancreas under sterile conditions and the fatal effect of total loss of pancreatic juice. *Jour. Exp. Med.*, 45:561-570 (Mar.) 1927.
4. Mann, F. C. and Bollman, J. L.: A method for making a satisfactory fistula at any level of gastro-intestinal tract. *Ann. Surg.* 93:794-797 (Mar.) 1931.

## ABSTRACTS

MANN, FRANK, AND BOLLMAN, JESSE L.

*Jaundice. A Review of Some Experimental Investigations. J. A. M. A., 104:371, Feb. 2, 1935.*

All methods for the production of jaundice experimentally have one thing in common, that is, the production within the animal of more bile pigment than is eliminated by the liver at the same time. True hemolytic icterus as seen in the human being has not been produced experimentally in animals. The jaundice that follows complete removal of the liver is of the hemolytic icterus type. Obstruction of the common bile duct or injury to the liver produces a jaundice which might be called hepatic.

The results upon the animal of the jaundice depends on three factors: The effect of the retained bile on the body cells, the effect of the alteration of the bile or its absence in the intestinal tract, and the effect of the liver injury which accompanies the jaundice. Of these factors the loss of bile from the intestinal tract has been the only one carefully investigated. Complete loss of bile is compatible with life for an indefinite period but adequate care and a suitable diet are necessary.

There is a marked tendency for jaundiced animals to develop peptic ulcers. Perforation of an ulcer is the chief cause of death of animals with complete obstructive jaun-

dice. There has been no increase in gastric acidity in these animals. It is thought that the jaundice reduces the resistance of the gastric and duodenal mucosa.

The addition of meat to the diet of dogs with complete biliary obstruction of more than three months duration will usually result in death in less than a week, but they will live for months on a diet of milk and syrup.

Usually after three months of complete obstructive jaundice the feedings of meat or beef extractives will produce rapid formation of ascites. Resumption of original diet will cause the ascites to disappear.

Bile pigment continues to be formed after the removal of the liver. Hemoglobin is undoubtedly the material from which it is made. The main site of bilirubin formation in the mammal seems to be in the bone marrow.

No important function has been ascribed to bilirubin.

Bile salts must be formed in the liver because after its removal no bile salts can be detected in the blood or urine.

Complete biliary obstruction reduces the bile salts excreted in the urine by one-half of that found in normal animals with biliary fistulas. Further injury to the liver reduces this amount in the urine and blood until they may disappear entirely.

Francis D. Murphy, Milwaukee.

## SECTION III—*Nutrition*

### Protection of Nutrition During the Use of "Elimination Diets"

By

ALBERT H. ROWE, M.D.\*

OAKLAND, CALIFORNIA

I HAVE always stressed the importance of assuring the proper intake of proteins, calories, vitamins and minerals in the "elimination diet" (1) which is taken for more than a week. I agree with Alvarez and Fineburg and others that absolute assurance of such a balanced diet is not necessary if the restricted diet has to be followed for only a few days. But in many definitely food sensitive patients, it is not possible to uncover the causes of their allergy rapidly, and diet trial must be continued for weeks or months until a diet which best relieves their allergy is obtained.

It is especially important to protect the patient against undesirable weight loss. Therefore where weight is low, patients must be told that they must eat plenty of the calorie carrying oils, sugars, and starches in their prescribed diets. Fortunately most patients maintain weight without such emphasis on calories. If weight tends to fall, it is wise to advise from one to four teaspoonfuls of prescribed oil in various foods with meals, and the same amount after meals to be taken as cod liver oil would be. In some cases, even more oil can be ingested without digestive disturbance. In addition, if attention is given to the inclusion of as much sugar and prescribed carbohydrate as the patient can tolerate, weight reduction can be prevented in practically all cases. If weight declines in spite of the physician's advice, it is practically certain that the patient is not cooperating in taking the requisite calories or that former habits of eating, lack of appetite, or indigestion prevent him from so doing. In such cases, I feel that a continuation of the "elimination diets" is not warranted, and that a general diet should be resumed, even though symptoms from allergy producing foods continue.

Emphasis moreover must be given to the necessity of assuring a proper protein intake. With milk, egg, and fish out of the diet, it is wise to insist that the patient take meat in fairly liberal amounts in some form at each meal, as suggested in the menus for my diets. McCollum (2) and McLester (3) especially have stressed the fact that a low protein intake over a long period results insidiously in decreased resistance to disease, lessened mental and bodily efficiency and stamina, early senility, and even in lessened fertility. Youmans (4) has reported internal edema, swelling of ankles and lowered serum proteins which

result from a low protein diet. In general there is an unfortunate prejudice against the ingestion of ample animal proteins which prompted Mosenthal and Boldman (5) recently to suggest an educational campaign to teach the public the importance of adequate animal protein in the routine diet.

The necessity of assuring a liberal intake of vitamins is more generally realized. The "elimination diets" which exclude milk and egg are moderately deficient in Vitamin D, which requires its addition in cod liver oil or halibut oil, or in viosterol. If natural or artificial sunlight is available, Vitamin D will be built up in the skin, making such vitamin therapy unnecessary except in the winter months. If fish is not in the diet, and especially if the patient is sensitive to cod liver oil, and sunlight is not available, then viosterol is necessary. Such viosterol is best prescribed in an oil which is included in the diet. Thus cottonseed sensitive patients should not take viosterol dispensed in cottonseed oil, and the same applies to corn sensitive patients with corn oil. Mead, Johnson and Company is preparing a viosterol in a soya bean oil for my patients who are on cereal free diets. Viosterol put up in sesame oil would also be suitable. Moreover, Vitamin D can be obtained through the use of irradiated foods. Since irradiated milk is not available to most food sensitive patients, at least at the start of their diet trials, it is advisable at times to irradiate certain foods, such as cereals or oils included in the patient's diet by exposing such foods under an efficient quartz light.

If the patient takes fairly liberal amounts of vegetables and fruit, a proper intake of Vitamins A, B, D, and G is probably assured. However, some children dislike and refuse vegetables, either because of whims or underlying allergy. Others refuse or have allergic reactions to many, and at times to all fruits. In these cases, the inclusion of yeast will take care of a deficiency in Vitamins B and G. It must be realized that yeast allergy rarely does occur, and at times is associated with positive skin tests to yeast. For a deficiency in A arising from inability to take green vegetables, especially carrots, spinach, and peas, the use of Carotene obtained from carrots may be indicated. In allergy, proper intake of Vitamin A seems important, since it may help to assure the integrity of the epithelial structures. If allergy exists to citrus fruits and a fair intake of green vegetables, especial-

\*Lecturer in Medicine, School of Medicine, University of California. Chief of Allergy Clinics at Alameda County and St. Mary's Hospitals.  
Submitted May 2, 1935.

ly of tomato is not ingested by the patient, deficiency of Vitamin C may occur. In rare cases, the taking of ascorbic acid ( $C^6H^8O_6$ ) may be indicated. This has been prepared from limes, and seems to be identical with Vitamin C, .01 gr. of it equalling 30 cc. of orange juice. With such attention, latent avitaminosis will be prevented. I agree with Alvarez (6) however, that the recent overemphasis of vitamin therapy for commercial advantage is to be discouraged.

Finally, with a milk free diet, there is usually a slight calcium deficiency, especially if liberal amounts of calcium carrying vegetables are not consumed. Sherman (7) has shown that from .7 to one gram of calcium in the diet is needed every day. He has stressed the fact that the average American dietary is deficient in calcium, and that a proper amount preserves the characteristics of youth and that it is essential for the proper growth and normal metabolism. Thus the addition of one-half to one dram of a calcium salt is advisable. Bernheim (8) and others feel that it is best absorbed during digestive rest, between meals or on retiring. The use of dicalcium phosphate supplies phosphorus as well as calcium in a ratio approximating that demanded by the body. Tribasic calcium phosphate serves the same purpose and is less expensive. Calcium gluconate and calcium lactate have also been recommended to supply necessary extra calcium. However, as an inexpensive source of calcium, calcium carbonate is of value. Sherman, in a personal communication, states that finely ground carbonate should be as effective, though more slowly absorbed than calcium lactate.

It must be pointed out moreover that important elements in foods, especially in fruits and vegetables other than vitamins and minerals, probably exist which

are not recognized today. Of interest is the recent emphasis of unsaturated fatty acids in body economy, as pointed out especially by Evans and Lepkovsky (9). The realization that chronic dietary deficiencies produce serious disturbances has been stressed by Minot (10) in an excellent article. He points out the importance of including the dietary history in every patient's record. This should include the habits of eating from childhood, the actual amounts of milk, egg, meat, vegetables, and fruits eaten through the years, together with the habits of exercise, walking and work, and the amount of strain, tension, or relaxation which have been routine.

These suggestions about the adequate and balanced diet have been offered to aid physicians who are using diet trial, and especially the "elimination diets" for the diagnosis and treatment of food allergy. Deficiencies are not apt to occur if the suggestions and detailed menus for the "elimination diets" and especially those for the revised ones (11) are accurately followed. Care must be taken not to eliminate foods to which dislikes or apparent idiosyncrasies exist which are the results of nervousness or prejudices. In such neurotics many foods are unjustly suspected and unwarranted limitations may be so numerous that very unbalanced and harmful diets result. Such diets may also occur when foods are eliminated on the basis of positive skin reactions. In these patients who are suspected of true allergy, it may be necessary however to exclude many separate foods or groups of foods during the diagnostic period. In such cases, care about the adequate inclusion of protein, calories, vitamins and minerals discussed in this article will prevent metabolic injury which might otherwise occur.

## REFERENCES

1. Rowe, A. H.: "Food Allergy, Its Manifestations, Diagnosis, and Treatment." *J. A. M. A.*, 91:1623-1629, 1928.
2. Rowe, A. H.: "Food Allergy, Its Manifestations, Diagnosis, and Treatment." *Lea and Febiger*, 1931.
3. McCollum, E. V.: "The Newer Knowledge of Nutrition", *McMillen*, 1928.
4. McLester, J. S.: "Nutrition and Diet in Health and Disease." *Saunders*, 1928.
5. Youmans, J. B.: Endemic Edema. *J. A. M. A.*, 99:883, 1932.
6. Mosenthal, H. O. and Moldman, C.: Diabetes Mellitus—Problems of Present Day Treatment. *Amer. Jour. Med. Sc.* 186:605, 1933.
7. Alvarez, W. C.: Is the Public Being Stampeded in Regard to Vitamins? *Amer. Jour. of Digestive Diseases and Nutrition*, 2:128, 1935.
8. Sherman, H. C.: Chemistry of Food and Nutrition, 4th Edition, *McMillen Co.* 1932.
9. Sherman, H. C.: Some recent Advances in the Chemistry of Nutrition. *J. A. M. A.*, 97:1425, 1931.
10. Bernheim, A. R.: Calcium Need and Calcium Utilization. *J. A. M. A.*, 97:1425, 1931.
11. Evans, H. M. and Lepkovsky, S.: Vitnl Need of Body for Certain Unsaturated Fatty Acids. *Jour. Biol.* 96:143, 1932.
12. Minot, G. R.: Three Cases of Chronic Dietary Deficiency. *Med. Clin. North Amer.*, 16:761, 1933.
13. Rowe, A. H. Revised Elimination Diets For the Diagnosis and Treatment of Food Allergy. *Amer. Jour. Digestive Diseases and Nutrition*, 1:387, 1934.

## ABSTRACTS

RUTH GILBERT AND M. B. COLEMAN, Albany, N. Y.

*Undulant Fever in New York State. Jour. Infect. Dis. Pages 305-312.*

Investigations into the incidence of porcine and bovine strains of *Bacterium abortus* in cases of undulant fever suggest a variable occurrence. In New York State, cattle or dairy products are the source of the infection in nearly all cases.

There has been a rising incidence of this disease for several years, but even so investigators doubt that a tenth of the cases which occur are recognized.

Symptoms of undulant fever vary greatly in severity and in nature. Six deaths have been reported by these

workers in the 400 cases studied. Some patients are acutely ill for months; others are always ambulatory. Clinical manifestations included chills, or chilly sensations; a remittent type of fever, with a slow pulse rate, fatigue, loss of weight, and constipation; diarrhea occasionally; headache; pain in the back; acute abdominal attacks; pains in the joints; and pulmonary symptoms. Slight anemia, with leukopenia and relative lymphocytosis, was common.

A large percentage of the patients infected have had no contact with cattle, but have drunk raw milk and cream.

General, efficient pasteurization of milk in New York State is urged.

J. Arnold Bargen, Rochester, Minn.

C. W. SCULL AND RALPH PEMBERTON.

*The Influence of Dietetic and Other Factors on the Swelling of Tissues in Arthritis; Preliminary Report. Ann. Int. Med., 8:1247, April, 1935.*

Scull and Pemberton, in a series of selected cases, have been able to show that the subsidence of swelling of tissues, pain and limitation of motion is accompanied by a net loss of water from the body. The authors are lead to suggest that disturbances of water distribution in tissues constitute significant factors in the dynamic pathologic changes of the rheumatic syndrome. In evaluating the role of dietetic and other factors they have found that the administration of several types of low calorie diets is associated with a net loss of water and with clinical improvement. Dehydrating diets, adequate in calories, high in protein, low in fluid and high in fat induced a net loss of water from arthritic patients with clinical evidence of improvement, and the suggestion is made that the relative increase of fat and protein metabolized on low calorie diets exerts a significant influence in the striking clinical effects frequently achieved. Recumbent rest is considered as acting, in part, by favorably influencing a shift of fluid from the tissues to the blood and lymph channels. Many seemingly unrelated factors which influence arthritis favorably when used within proper limits, such as dietetics, recumbent rest, heat and massage, may act in part by favoring fluid removal from tissues. Attention is directed to the fact that a negative water balance contributes to recovery from both atrophic and hypertrophic arthritis. This suggests that both types of arthritis arise, in part, from similar or comparable premises; and further, that rigid restriction of many therapeutic measures, especially those here mentioned, to one type alone is unwarranted. The relationships pointed out do not imply that dehydrating measures alone constitute a therapeutic escape from arthritis. Vigorous sweating, purgation or diuresis have long been known to be of only limited value, and even dangerous. So far as changes in the distribution of tissue fluids in arthritis may be desirable, they should be achieved by the more sustained and "physiological" influence and measures discussed by the authors. Further justification is afforded for the controlled use of dietetic measures in the treatment of arthritis. The reader is again cautioned as to the dangers involved in uncritical employment of this agency.

Samuel Morrison, Baltimore.

JOHN M. FLYNN, M.D.

*The Changing Cause of Death in Diabetes Mellitus. (From the Medical Clinic of the Peter Bent Brigham Hospital, Boston).*

The records of all the cases of diabetes mellitus dying in the Peter Bent Brigham Hospital between its opening in 1913 and the commencement of the insulin era in 1923 were analyzed with the following summarized conclusion:

1. "The annual mortality of new cases varied so much from year to year as to make conclusions with regard to the value of treatment, as it affected the hospital mortality of diabetes during any one year, of but little value.

2. Diabetes became less severe as the age at which symptoms were first recognized became greater, although increasing years did not necessarily preclude a severe form of the disease.

3. There were four common causes of death. These were: (a) Coma, with or without terminal infection; (b) Sepsis; (c) Cardiovascular renal disease, including gangrene; (d) pulmonary tuberculosis."

There were 562 cases admitted from 1913 to the end of 1922 and 49 died in the hospital. From 1923 to 1933, 917 cases were admitted and 66 died in the hospital. The mortality rate of the pre-insulin period was 9% and that of

the post-insulin period 7%. The most striking feature to be observed in a comparison of the two groups of cases is that fatalities in the younger age group now appear to be much less frequently met with than formerly. The previous study showed 21 deaths in persons below their 40th year, whereas the present study shows but 7 or in terms of percentage, 38% of the deaths in the earlier series occurred in patients below 40, while but 14% of the younger cases in the present series have been fatal. This is due to insulin.

In the age group from 61 to 80 the average duration of life was 8.1 years in the earlier series and 5.7 years in the present study. Two striking differences are to be seen between the fate of the pre-insulin diabetic and the diabetic of today. Deaths from coma, sepsis and tuberculosis have shown a marked decrease, whereas those due to cardiovascular disease and its sequelae have shown a marked tendency to rise. Among the conclusions drawn are that cardiovascular disease has shown an increase in frequency; unusual complications have remained practically unchanged. The mortality rate of new cases of diabetes in this clinic has decreased from 9% prior to the introduction of insulin to 7% during the period of insulin therapy. The present tendency is for coma and sepsis to be eradicated. Our present mode of treatment appears to have no effect upon the form of cardiovascular disease which is seen in diabetic patients.

Allen A. Jones, Buffalo.

SPIES, TOM D.

*The Treatment of Pellagra. J.A.M.A. 104:137 (Apr. 20, 1935).*

It has been recognized that the prognosis in the patient severely ill with pellagra is exceedingly grave. The mortality rate in such a group of cases treated in the hospital with highly nutritious diet and yeast was 54 per cent. More recently a second and larger series of such cases showed a mortality of only 6 per cent. The striking difference in mortality rate is the reason for the present paper.

The therapeutic measures the author stresses as important in this paper are as follows:

Adequate professional and nursing care. A diet of 4000 calories a day must be given.

Yeast is highly efficacious in the treatment, 75 to 100 grams daily in the powder form. This may be given in divided dosage.

Ventriculin in doses of 200 grams daily is just as effective as yeast and easier to take.

Wheat germ in 250 to 300 grams is also efficacious in the treatment.

Liver extract orally or parenterally may be used.

Parenteral liver extract is used when the patient is dangerously ill.

Stomatitis and glossitis quickly improve as the condition improves.

Tincture of opium is useful in the treatment of the diarrhea.

Vomiting must be treated by frequent small feedings. Abdominal pain if it is not due to surgical condition can be controlled by tincture of opium.

Nervous system involvement and peripheral neuritis require sedatives and special care in feeding to keep the nutrition up.

Anemia is handled with diet and in other cases with large amounts of iron.

Dermatitis is treated with mild antiseptic solutions used as soaks or on sponges.

Relapses must be watched for after return to health. The patients should be seen at least once a month to make sure that they are taking and assimilating an adequate diet.

Francis D. Murphy, Milwaukee.



BERGER, EDMUND H., AND BINGER, MELVIN W.

*The Status of the Kidneys in Alkalosis. J.A.M.A. 104:1383 (April 20, 1935).*

The authors discuss seven cases treated for peptic ulcer with the use of alkali in whom definite symptoms and chemical evidence of alkalosis developed.

The symptoms complained of in this group of cases were distaste for milk, anorexia, nausea, and vomiting, weakness, nervousness, mental confusion, dull steady headache, polydipsia, polyurea, numbness and tingling, cramps, and in several instances tetany.

The carbon dioxide combining power of the blood ranged from 69 to 84 volumes per cent.

The authors stress that the condition comes on slowly and that it is relatively uncommon.

They stress that the status of kidney function be carefully checked before alkaline powder therapy is used. If kidney impairment exists, alkaline therapy will probably be unsatisfactory.

Mucin or tribasic calcium phosphate may be used in some of these cases advantageously.

The question of renal damage from prolonged use of alkali therapy is not settled.

In five out of the seven cases here discussed evidence of impaired renal function was present after the alkalosis had been adequately controlled.

Impaired renal function is important etiologically in alkalosis and must be given consideration before instituting alkali therapy in peptic ulcer.

Francis D. Murphy, Milwaukee.

MACKIE, THOMAS T., AND HENRIQUES, MADELEINE.

*Ulcerative Colitis. II-Deficiency States. J. A. M. A., 104:175 (Jan. 19, 1935).*

In a group of seventy-five consecutive cases of ulcerative colitis varying in degree from mild localized proctitis to advanced and extensive involvement of the entire colon, forty-seven cases showing indications of deficiency states were encountered.

The most common manifestation was the change in the mucous membrane of the tongue. This was found in forty-six patients.

Changes in the buccal mucosa were noted in four patients. Abnormal skin conditions were found in eleven cases.

Blood chemistry changes were noted in seven cases. Three of these patients showed inversion of the albumin-globulin ratio and extensive edema.

In thirty-nine cases anemia was present.

Peripheral neuritis occurred in one case.

The author feels that deficiency states are important factors in the pathologic physiology of ulcerative colitis.

Francis D. Murphy, Milwaukee.

ALICE BERNHEIM AND J. H. GARLOCK.

*Parathyroidectomy for Raynaud's Disease and Scleroderma. Department of Surgery, Cornell Med. School, Ann. Sur., Vol. 101, No. 4, April, 1935.*

As a result of observations which cover a number of years the authors have formed the opinion that disturbances in calcium metabolism are factors in the development of Raynaud's Disease and other vasospastic conditions. Calcium deficiency in the diet, common in adults and producing a negative calcium balance, may cause in certain individuals an abnormal sensitiveness to vasospasm. In patients with thrombo-angiitis obliterans, Raynaud's Disease or arteriosclerosis, vasoconstricting stimuli as cold, worry, fatigue, over-exertion and tobacco may produce pain, undue coldness, intermittent claudication and discoloration of the extremities.

It is not known exactly how disturbances in calcium metabolism produce the various manifestations of vasospas-

tic conditions. The constitutional factor must play an important role since it is observed that individuals react differently to disturbance of calcium metabolism—some may show merely a vasospasm of peripheral vessels as in Raynaud's Disease, while others may show a generalized or localized scleroderma. Others show nephrolithiasis or nephrocalcinosis while in others the change may be due to changes only in the bony skeleton producing generalized decalcification.

The authors point out that the proper understanding of the rationale for parathyroidectomy in these conditions begins with the assumption that one of the functions of the parathyroid glands is to maintain a constant serum calcium level of about 10 to 10.5 mgs. per 100 cc. With long deficiency in calcium intake the glands become hypertrophied as a result of thin increased physiological activity in withdrawing calcium from the bones to the blood.

Many such patients will respond favorably to an adequate calcium intake but the authors feel that if there is no amelioration of symptoms, parathyroidectomy should be resorted to. They give case histories of six patients who failed to respond to increased calcium intake and who showed spectacular and immediate amelioration of symptoms following removal of one or two of the parathyroids. They found that the removal of one or more of these glands did not result in a compensatory hypertrophy of those remaining. No post-operative tetany was observed due to adequate pre and post-operative calcium administration.

Charles T. Sturgeon, Los Angeles.

MACKIE, THOMAS T., AND POUND, ROBERT E.

*Changes in the Gastro-Intestinal Tract in Deficiency States. J.A.M.A. 104:613 (Feb. 23, 1935).*

In studying a group of seventy-five cases of ulcerative colitis, deficiency states of varying degree were found in sixty-three per cent of the group. A history of defective dietary was seldom elicited. Too rapid a passage of food constituents through the intestinal tract or abnormalities of the small intestine producing defective absorption of the product of digestion was given possible etiologic significance.

Roentgenographically, changes were demonstrated in twenty-nine out of thirty-seven cases of chronic ulcerative colitis. Edema of the mucous membrane, disorganization of motor activity and hypotonicity of intestinal musculature could account for the changes noted radiographically.

The suggestion is made that these changes in the small intestine are related to the deficiency states and perhaps play a part in their development.

Francis D. Murphy, Milwaukee.

REDVERS, THOMPSON, Quebec, Can.

*Elimination of Brucella Abortus With the Milk of "Carrier" Cows. Jour. of Infect. Dis. Pages 6-11.*

Knowledge of the group of organisms classified under the generic name of Brucella has been accumulated since its discovery thirty-six years ago. Interest has been directed toward a study of its natural habitat, modes of dissemination, and control of the infection which it produces. So far the infection must still be considered in the same category as tuberculosis.

The milk of ten high-producing cows, which never manifested clinical symptoms of infectious abortion, but whose blood serum showed significant agglutinins for Brucella abortus was examined for the presence of Brucella abortus at intervals of thirty days over an entire lactation period.

The study demonstrated that Brucella abortus may be constantly eliminated with the milk of cows classified as "healthy carriers."

J. Arnold Bagen, Rochester, Minn.

## SECTION IV—Roentgenology

### Diaphragmatic Hernia: with a Report of Ten Cases of Oesophageal Orifice Hernia\*

By

KATHERINE S. ANDREWS, M.D.  
BOSTON, MASSACHUSETTS

#### HISTORY

THE first description of any type of hernia through the diaphragm is that of Ambrose Paré (1) who described two traumatic hernias in 1610. Thirty-six years later, Fabricius Hildanus (2) described another traumatic case, and 1698 Riverius (3) described the first congenital diaphragmatic hernia. Morgagni (4) wrote the first monograph in 1769, and in 1824 Sir Astley Cooper (5) added an account in his "Treatise on Hernia." From 1853, when Bowditch (6) presented 88 cases from the literature, there has been a slowly, but steadily growing interest in diaphragmatic hernia as attested by the numerous papers appearing in both English and foreign literatures. However, it was not until 1903 that the first case of para-oesophageal hernia was described by Andrew (7): this hernia was discovered during a post-mortem examination in the dissecting room of the Aberdeen university. In recent years, improved methods of radiographic technique demonstrated by Berg and Akerlund and their associates, have made it possible to study this condition with accuracy and have added considerably to our knowledge of it.

#### INCIDENCE

The incidence of diaphragmatic hernia is hard to determine since there is great discrepancy in published reports. According to Arnsperger (quoted by Folk-nord) (8), prior to 1908 the diagnosis had been made only ten times on living persons. In 1915 Kienboeck (9) reported 3 cases diagnosed and confirmed by necropsy and MacMillan (10) (1920) found 3 cases in 15,000 radiographic examinations in United States Army General Hospital No. 1. Rendick (11) reported 2 cases in 5033 clinical examinations in Bellevue Hospital. From the year 1920 on, larger series of cases have been reported. L. B. Morrison (12) reported 42 cases out of 3500 (1925) gastric cases studied. Pan-coast and Boles (13) report (1924) 16 cases (one traumatic) out of 9000 gastro-intestinal examinations. Akerlund (14) reported 30 new cases in 1926, and Ritvo (15) reported 60 cases observed over a period of five years. In the Mayo Clinic (16) from 1900-1925, 30 cases were recognized and 19 were confirmed

at operation. From 1925-1933, 147 cases were recognized, and 60 patients operated on; *i. e.*, five times as many cases in last 8 years as in preceding 24 years. In 1931 Hedblom (17) again summarized the literature and tabulated 1435 cases, 190 of which were hernias of the oesophageal hiatus. From these reports it is obvious that the incidence of diaphragmatic hernia in the literature is increasing rapidly, probably because it is now possible with improved radiographic methods to demonstrate the presence of these hernias more easily. Some radiologists believe the presence of small oesophageal orifice-hernias to be a normal occurrence in advanced age. Schatzki (18) found them in 22 out of 30 random subjects between the ages of 65 to 83.

#### DEFINITION AND CLASSIFICATION

Hernias of the diaphragm must be distinguished on the one hand from eventration of the stomach, and on the other from thoracic stomach. In the former, the diaphragm is abnormally high, but the stomach always lies below it. In the latter, the stomach always lies above the diaphragm, and the oesophagus does not pass through it, the opening usually occupied by the oesophagus being occupied by the duodenum. (Le-Wald (19)). In diaphragmatic hernias, the abdominal organs may be found at times above the diaphragm, and at times below. Almost any abdominal organ may participate in diaphragmatic hernias: the colon, liver, pancreas, spleen, but in the majority of cases the stomach alone is implicated.

Hernias of the diaphragm have been variously classified. Richards (20), 1923, has classified them from an embryological point of view as being "true" hernias or "false" hernias,—the true hernias being those with a hernial sac, and the false those without a sac. These, again, he subdivides into congenital and acquired hernias. 90 per cent (he states) of all cases are "false" hernias.

Ritvo (15) classified diaphragmatic hernias into "congenital" and "acquired," the congenital hernias being due to maldevelopment of the diaphragm, or to the delayed descent of the stomach, and the acquired hernias being due to an increase in intra-abdominal pressure. By other observers, they are classified as "traumatic" or "non-traumatic" hernias. But as Harrington has pointed out the numerous classifica-

\*From the Gastro-intestinal Clinic of the Boston Dispensary and the medical service of Dr. Joseph H. Pratt.  
Submitted, May 17, 1935.

tions are of academic interest only and it is difficult or impossible to distinguish them clinically.

### ETIOLOGY

The importance of an embryological factor in the etiology of these hernias has been stressed by numerous writers. The consensus of opinion seems to be that in congenital hernias there must be either a delayed descent of the stomach from the thorax with simultaneous shortening of the oesophagus, or else a maldevelopment of the diaphragm, with improper fusion of its parts, or with abnormality in the muscle fibres themselves. Ritvo (15) 1930, has discussed these points in detail and more recently Morrison (21) *et al.* (1934) have done likewise. In the acquired hernias there is thought to be some underlying weakness of the musculature which makes it possible for an increase in intra-abdominal pressure such as is present in pregnancy, constipation, obesity, even though the pressure be not great, to force the abdominal organs into the chest cavity.

Non-traumatic herniation may occur theoretically in any of the normal openings of the diaphragm, but actually most hernias present themselves through the oesophageal opening. Ritvo (15) states that hernias through the vena cava or aortic opening are unknown, and Healy (22) points out that this is probably true because the oesophageal opening is the only muscular one in the diaphragm, the others being made up of tendinous attachments.

*Hiatus Hernias:* In 1911 Eppinger (23) in his comprehensive monograph on the diaphragm reported 635 non-traumatic diaphragmatic hernias, and found 55 of these to occur through the right dome of the diaphragm, and 11 through the oesophageal opening. But, more recently, Akerlund (14) has demonstrated oesophageal "hiatus hernias" to be 6 or 7 times as frequent as all non-traumatic diaphragmatic hernias combined. The improved radiographic technique advocated by Fofssell and his school recently has made it possible to verify the accuracy of Akerlund's observation. The 10 cases reported below fall entirely into this group of oesophageal orifice hernias.

Akerlund (14) classified all such hernias through the oesophageal orifice in 3 groups, on an anatomical basis.

1. Oesophageal hiatus hernias with congenital shortening of the oesophagus.
2. Oesophageal hiatus hernias without congenitally shortening of oesophagus in which the oesophagus does not form part of the hernia. (*i. e.*, Para oesophageal hernias.)
3. Oesophageal hiatus hernias in which the oesophagus is not shortened but in which the distal portion of the oesophagus is a part of the hernia contents.

Of these three the last group is the most common, the first the least common.

### SYMPTOMS

Oesophageal orifice hernias do not always present symptoms, it is now well understood. The growing literature on the subject from radiologists, indicates that many small hiatus hernias, discovered in the course of routine examination for other conditions, are entirely without symptoms. This is apt particularly to be true in advanced age as emphasized by Schatzki (18). When these hernias do present symptoms they may be of two types, *i. e.*, those with *symptoms referable to the abdomen*, and those with *symptoms referable to the thorax*.

The case histories reported below, illustrate in detail the symptomatology as presented by our group.

*Pain or abdominal discomfort* (often limited to the epigastrium) was present in all our cases except two (Cases V and VII). There was no definite time-relation of pain to food, and no constant relief by food; indeed eating usually aggravated the discomfort. It was sometimes severe (as in Cases VI and X) but was usually not severe. Paneoast and Boles (13) note, in their study, that pain may be so severe as to simulate biliary colic, and may have the same radiation. It may be even excruciating enough to suggest angina pectoris (Case VI). It is easily conceivable that such might be so when the hernia is held fixed in the oesophageal opening. The most significant fact about pain in our series was that it often had a postural relation, and sometimes could be relieved by assuming the upright position.

*Dysphagia* was noted in three of our cases (Cases I, VIII and X). Wagner (24) has emphasized it in his study, as has also Healy (22). *Nausea and vomiting* were outstanding symptoms in seven of our ten cases and had very definite relation to position. In Case V the statement that vomiting could be affected by bending forward led to the clinical diagnosis before radiographic studies were made. *Eruptions of gas* (Cases III, IX and X), and *regurgitation* (Cases VII and VIII) were noted less frequently. *Haemetemesis or melena* was not noted in any instances, though Hedblom (17) gives bleeding as a symptom in 8 of his 229 cases.

Of *thoracic symptoms*, palpitation was an outstanding symptom in Case IV and *dyspnea* in Case I. These cardio-respiratory symptoms seem most likely to occur when the hernia is large or well filled, or when there is associated cardiac disease such as aortitis or cardio-sclerosis. *Cough* was noted (Cases I and III) and has been emphasized as occurring especially in children by Truesdale (25); it is apt to occur in paroxysms and is non-productive.

Ulcers of the stomach either in the herniated portion, or in the stomach below the hernia, or in the duodenum have been described by Key (26), Harrington (27), Kransjö (28) and others. In these cases the symptomatology of peptic ulcer may dominate the picture. We observed none of these in our group.

*Secondary anemia* in association with ulcer and hiatus hernia has been noted by Gardener (29) and others, but it has also been noted in patients without demonstrable erosion or ulceration as Bock (30) has recently pointed out. Case X illustrates this fact.

### DIAGNOSIS

As has been intimated, the diagnosis of this condition is made by radiological examination. However, familiarity with the clinical picture sometimes may lead one to suspect the presence of hiatus hernia. In Case V the presumptive diagnosis was made by the clinician and confirmed by the radiologist only by having the patient bend forward several times, thus forcing the sac to protrude above the diaphragm and to fill with barium. The story of symptoms which come and go with change of posture seem to us very suggestive. Truesdale (25) recently has (1931) pointed out that clinicians usually fail to consider the possibility of hiatus hernia in differential diagnosis.

**Differential diagnosis:** The case histories appended indicate the chief conditions to be considered in the differential diagnosis. *Oesophageal obstruction* from organic disease is suggested by the dysphagia of Case I, for instance. Case VI, in its periodicity, time-relation of symptoms to, and relief by food, makes one think of *peptic ulcer*. The picture presented by Case V might well be ascribed entirely to a *neurosis*; and that of Case X to *gall-bladder disease* with stones. As is noted, severe *cardiac disease* is suggested by the history of Case VI. These last two possible conditions, *i. e.*, cholelithiasis and angina pectoris, are the affections most likely to be confused with incarcerated hernia of the oesophageal orifice. It should be emphasized, perhaps, that as one becomes more and more familiar with the clinical picture of hiatus hernia, it assumes the aspects of a definite symptom-complex which can often be suspected by the clinician even before it is confirmed by radiologic examination.

**Röntgen Data:** The best radiological technique for the examination of the patient seems to be that in which the patient is examined in both prone and erect postures, and turned freely from side to side, and from front to back, while under the fluoroscope. Observation while the diaphragm is held in deep inspiration often is helpful. Important in establishing the diagnosis and in differentiating hiatus hernia from epicardial dilatation of the oesophagus, is the tracing of the mucosal folds of the stomach into the herniated sac. This can best be done by studying with the "relief" method of Forsell and Berg.

### TREATMENT

It must be emphasized that many hiatus hernias require no special treatment, since many, especially in older people, it now appears, are asymptomatic and are discovered only in the course of routine examination. However, others do produce symptoms, as in the cases cited, and an effort must be made to give relief. Medical treatment often will suffice. This consists chiefly in diet. Small frequent feedings of easily digested food have been most helpful in our group. An effort should be made to eliminate those food-stuffs which ferment easily or cause the production of gas. In Germany, carbonated waters have been given in an attempt to balloon-out the fundus of the stomach and so prevent its herniation. Our own results in this respect have not been successful. It is important to instruct the patient to maintain the erect posture for an hour or two after each meal. Associated conditions, such as ulcer and anemia, must receive their usual treatment. In those cases unrelieved by a medical regime, or in those patients presenting severer symptoms, surgery must be resorted to. Incarceration always calls for immediate surgery.

The approach in surgery may be either through the thoracic cavity or by the abdominal route. Both methods give good results in the hands of experienced surgeons. Truesdale (25) in 1931 reports 12 cases of diaphragmatic hernia (9 children and 3 adults) operated on by the thoracic method with only one death,—that in an adult from pneumonia on the seventh post-operative day. And in 1934 he reported on six cases of the oesophageal orifice type operated on by the transthoracic approach without a fatality. (25) Hedblom (17) in 1925 studied 378 operated cases of her-

nias through the diaphragm, nineteen from the Mayo Clinic, and the rest from the literature. Of 126 operations for acute incarceration, sixty-seven died (mortality 53%); and of 252 without incarceration fifty-nine died (mortality 23.4 per cent). Harrington (31), up to November, 1928 had only one death (from pneumonia) in 21 cases. In 1929 he reported fourteen more cases (32) operated upon by laparotomy with two deaths, one from cardiac and one from pulmonary complications. Some of these cases reported were cases of hernias following injuries (such as automobile accidents), so, that one might expect a higher mortality than in operations of election.

Phrenectomy, phrenicotomy, or phrenic emphraxis are sometimes used as palliative measures or as preliminary measures for operations in these cases. Harrington (32) feels that the pumping action of the diaphragm is an important factor in producing the symptoms. Phrenectomy paralyzes the diaphragmatic muscle and stops this pumping action. Also by these means nerve communications are destroyed, which destruction prevents reflex cardio-spasm, and shoulder pain. Key (26), as early as 1924 advocated neurectomy as a cure for ulcers associated with diaphragmatic hernia in an effort to mobilize the diaphragm and so reduce bleeding and symptoms. Goetze (33) seems to have been the first to simplify suturing of the diaphragm by chilling of the phrenic nerve with ice (done in children) in 1925. Two years later Lemons (34) suggested phrenic neurectomy as a preliminary measure in more radical operations. In 1929 Harrington (32) reported three cases in which he had excised the phrenic nerve with some success. These advances in surgery indicate that one should not hesitate to resort to operation in cases in which the symptoms persist in spite of medical treatment.

### SUMMARY

1. Herniation of the stomach into the chest cavity is discussed with special emphasis upon the hernias of the oesophageal orifice.
2. Ten cases of hiatus hernia are presented in the hope that they may serve to make clearer the symptomatology of this not uncommon condition.\*

### CASE REPORTS

**Case 1.**—G. G. Aged 44. American. Janitor. This patient was well until four years before admission. At that time he first developed a sense of discomfort under his sternum which he described by saying "it seems at times as though the food does not have time to go down to the stomach," or, "it seems as though there is a ball in my stomach which moves up and down." This "ball" he stated rose in his throat and often choked him when he was eating, and at such times he grew very short of breath, the discomfort became more severe, and at times amounted to actual pain which was located under the sternum and about both costal margins. Usually when the pain occurred it came on about a half hour after eating and lasted several hours. Sometimes it awakened him at night. It was not relieved by food or by soda, but at times it was relieved by aromatic ammonia. In addition to these symptoms he stated that he was sometimes awakened from sleep by fits of non-productive coughing, and a sense of suffocation. These symptoms he could always relieve by getting up and walking about. There were various other

NOTE: In each case reported, the radiologic diagnosis was made by Dr. Alice Ettinger. I wish to express my appreciation to Dr. Ettinger for her help and for her permission to reproduce the roentgenograms.

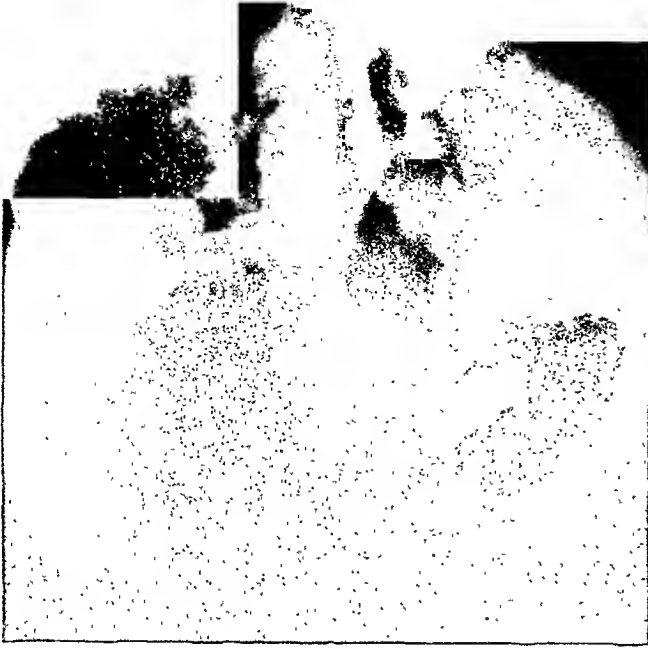


Fig. 1. Case II.

unrelated symptoms such as dizziness, insomnia and headache.

**PHYSICAL EXAMINATION** showed a rather stocky man, apparently in good health, with wide spread lesions of scabies. The heart and lungs were apparently entirely normal. Blood pressure was 134/80. Examination of the abdomen revealed slight tenderness in the epigastrium and in the right upper quadrant. Knee jerks and pupillary reflexes were normal.

Urinalysis was normal.

Hinton test was negative.

Blood count was 4,625,000 red cells per cubic millimeter and 9,300 white cells; 96% of hemoglobin (Sahli), and a normal differential.

Gastric analysis (Ewald meal) showed no free hydrochloric acid, but a total acidity of 25.

Stool examination for occult blood was negative.

Orthodiagram showed slight enlargement of the heart to the left.

Electrocardiogram was reported as normal.

**Roentgenogram** of the gastro-intestinal tract revealed a walnut size dilatation at the lower end of the oesophagus, obviously not an epicardial retention, but a herniation of the stomach mucosa through the oesophageal opening.

**COMMENT:** This patient's description of his symptoms is most graphic. His paroxysms of nocturnal coughing and suffocation, it is interesting to note, were relieved by assuming an erect posture.

**Case 2.**—K. C. Aged 67. Canadian. Coal Miner. This patient came in to the clinic complaining of a burning sensation under the sternum which radiated upward toward his neck, and which had been present intermittently for ten or twelve years. It came on chiefly at night time, sometimes awakening him from sleep and being always definitely worse when he was in the recumbent position. Associated with the substernal burning there was often a feeling of nausea but no vomiting. There was also at times slight difficulty in swallowing, even liquids causing distress. There was no time relation to meals and no relief by ingestion of food. He had found, however, that he could obtain definite relief by bending forward and regurgitating his last meal.

**PHYSICAL EXAMINATION** was essentially negative, except for some sclerosis of the peripheral arteries and some shortening of the right leg, due to an old injury.

Urinalysis was normal.

Hinton test was negative.

The blood count was normal.

Gastric analysis showed free acid of 61, a total acidity of 73.

Stool examinations were negative for occult blood.

A **roentgenogram** of the gastro-intestinal tract revealed an orange-sized herniation of the stomach through the oesophageal hiatus. This was observed almost immediately and was seen in both upright and recumbent positions.

**COMMENT:** The relation of this patient's symptoms to posture is striking, as is the fact that he could relieve himself by bending forward and regurgitating food. Note also slight dysphagia.

**Case 3.**—C. W. Aged 74. American. Housewife. This patient's symptoms began twenty years ago. They consisted chiefly of epigastric discomfort which came on one to one and a half hours after meals, or in the early morning. It was located immediately below the xiphoid and did not radiate. It did not occur after every meal or even every day, but in the twenty years there had been no periods of distinct remissions and no periods of long relief. At the time of admission the distress was distinctly less troublesome than it had been four years before. In the earlier years vomiting usually accompanied the burning sensation, the food coming back in small quantities and in an undigested state. In recent years, however, vomiting had been less troublesome. Eructations of gas occurred also at times. All these symptoms, she stated, were most likely to come on when she was lying down. She suffered from no other distress, except a slight, non-productive cough present only occasionally. Sixteen years before admission, a gastro-intestinal series was reported as showing a herniation of the stomach through the diaphragm; four years before another gastro-intestinal series was reported as showing a gastric ulcer on the posterior wall. Two subsequent radiographic examinations, however, did not reveal the ulcer.

**PHYSICAL EXAMINATION** showed an extremely well preserved woman with early cataracts in both eyes. The heart and lungs were entirely normal. Blood pressure was 154/88. The abdomen was tympanitic to percussion, but otherwise entirely natural. The pupillary and knee reflexes were normal.

Urinalysis was normal.

Hinton test negative.

There was 92% of hemoglobin; 4,700,000 red blood cells; 7,300 white blood cells and a normal differential count.

Fractional Ewald meal showed a fasting achlorhydria but at the end of sixty minutes free acid reached 46 with a total acidity of 62.

Stool examinations were negative for blood by the benzidine test.

**Gastro-intestinal Roentgen** series showed an apple-sized herniation of the stomach mucosa through the oesophageal opening. There was also a diverticulum about the size of a walnut on the inferior surface, near the duodenal-jejunal flexion. The examination was otherwise negative.

Laboratory studies showed a blood sedimentation rate of 19 millimeters at the end of one hour.

**COMMENT:** This patient may well illustrate that group of cases in which hiatus hernia and peptic ulcer are associated. It makes clear the difficulty of differentiating these two conditions on a basis of history alone.

**Case 4.**—J. G. Aged 65. Jewish. Housewife. This patient was admitted complaining of palpitation, and "pains about her heart," and discomfort in the epigastrium. These had been present about a year. Palpitation came on in attacks without relation to exertion, appearing often while she was sitting at rest. With the palpitation she suffered at times, moderate or severe pain under the



Fig. 2. Case IV.

sternum and over the praecordial region. This, together with the pounding of her heart, had been severe enough and terrifying enough to make her call a doctor on two occasions; hypodermic medication was given for relief. There was no dyspnea while walking on a level, nor on climbing one flight of stairs and the patient slept comfortably with one pillow. No history of cough, nor of peripheral oedema. In addition to these symptoms, she complained also of some epigastric burning and discomfort relieved by soda bicarbonate. This, was not marked, had no relation to meals, and was not associated with nausea or vomiting. Constipation was troublesome. There was a loss of ten pounds in weight in three years. Vision, she said, was slowly failing.

PHYSICAL EXAMINATION revealed an elderly, gloomy woman with cataracts in both eyes, coated tongue and a lipoma above the right clavicle. The chest was emphysematous in type but the lungs were clear on physical examination. Examination of the heart showed it to be slightly enlarged to percussion, the right border measuring 2 centimeters and the left 13 centimeters from the mid sternal line. The rate was 98, and the rhythm showed frequent extra systoles; there were no murmurs; A2 was accentuated and the quality of the sounds was only moderately good. Blood pressure was 150/85. Peripheral blood vessels showed moderate sclerotic changes. Except for a small umbilical hernia, the abdomen was not remarkable. Both legs had small varicosities but the reflexes were normal.

Urinalyses were normal except for a trace of albumin. Hinton test was normal.

Blood count showed 80 per cent of hemoglobin, with 3,900,000 red cells and 7,700 white cells. Differential count was normal.

Stool examination was negative for occult blood.

Electrocardiogram reported T-wave flattened in all leads, and the regular interposition of ventricular extra systoles.

An orthodiagram showed the heart slightly enlarged with the aorta widened and tortuous.

A Graham Test reported the gall bladder to be normal.

A gastro-intestinal Roentgen series showed a hernia about the size of an apple through the oesophageal orifice. It was otherwise entirely normal.

COMMENT: This patient illustrates well the group of symptoms referable to thoracic organs which may be produced by hernias through the oesophageal opening. Electrocardiogram and orthodiagram demonstrate the presence of some organic changes of the cardio-vascular system, but the history of attacks suggests that the protrusion of the stomach into the chest space and may have initiated the cardiac symptoms.

Case 5. J. R. Aged 68. American. School teacher. This patient gave a confused story with multiplicity of complaints. Chief among these were symptoms referable to her joints and to her gastro-intestinal tract. Almost constant dull, aching pain in her knees, followed an accident in 1923, resulting in removal of a semi-lunar cartilage. Roentgenograms of the knees showed proliferative changes about the joint with narrowing of the joint spaces. A diagnosis of chronic arthritis was made and among other therapeutic measures a diet was prescribed. She then began to complain of vomiting, stating she could not eat fruit, fish, eggs and various other foods without vomiting immediately. There was little discomfort and no pain associated with this. The vomiting came on almost always after she went to bed. She stated that she could invariably produce it by bending forward. Bowels had a tendency to be loose; averaged seven or eight stools a day. Her dietary history was one of irregularity and inadequacy, but there had been no loss of weight.

PHYSICAL EXAMINATION was essentially negative except for Heberden's nodes on the fingers and some limitation, and crepitation, on motion in both knees.

Urinalyses were normal.

Laboratory studies showed negative blood serology.

Blood count showed 100% hemoglobin, 4,890,000 red cells; 6,675 white cells, and a normal differential count.

Gastric analysis showed free hydrochloric acidity 53, total acidity of 84.

Stool examinations were negative for occult blood.

Sensitization tests were entirely negative.

A psychological examination revealed an eccentric personality but no psychosis.

Gastro-intestinal roentgenograms at first seemed normal, there being no evidence of hernia in a recumbent position



Fig. 3. Case V.



or in deep inspiration. She was then asked to bend forward, and immediately afterward the hernia was visualized, with normal stomach mucosa easily recognized in it. The rest of the examination was entirely negative.

**COMMENT:** In this case it is obvious that all the patient's complaints cannot be due to the hiatus hernia; however, her history of vomiting only in a recumbent position, or after bending forward can easily be explained by the hernia.

**Case 6.**—S. D. Aged 60. Italian. Scissors grinder. This patient, about two months before admission, while climbing the stairs to the elevated railway, was seized with a very severe pain in his chest, chiefly under the sternum but also along the left costal margin. He had to be taken home and put to bed, where he remained about two weeks. Since that time he has had a number of similar attacks of severe substernal pain. These, however, were not always related to exertion, but came on at times, he insisted, soon after eating. The pain was paroxysmal in character; it had no time-relation to food, was not relieved by food. It has been severe enough to make him call a local physician. In addition to the attacks of severe pain he complained of "stomach trouble" which has been present on and off for ten years. By this he meant a feeling of discomfort in the epigastrium and under the sternum which came on one or two hours after eating and was relieved a little by food or by soda. There were no nausea and no vomiting with this. Some eructation of gas, no loss of weight. No symptoms referable to any other system.

**PHYSICAL EXAMINATION** showed an excitable, elderly, Italian man with marked dental cavities and pyorrhea and moderate sclerosis of the peripheral blood vessels. On examination of the heart, the apex beat was not seen or felt in any position. The right border measured 2 centimeters and the left 12.5 centimeters from the mid sternal line; the sounds were of good quality, the rhythm was regular, the rate was 72, no murmurs were heard. Blood pressure was 156/84. Lungs were entirely negative. The abdomen was natural.

Urinalyses were normal.

Hinton test was negative.

Blood count showed hemoglobin (Sahli) 95 per cent, 11,000 white cells, 4,705,000 red cells, and normal differential count.

An Ewald Meal reported normal motility with a free hydrochloric acid of 50 and a total acidity of 77.

Graham test was normal.

An electrocardiogram showed beginning partial A-V block, but no evidence of coronary disease.

An orthodiagram showed the heart moderately enlarged in all diameters (consistent with arterio-sclerotic heart disease.)

A roentgenogram of the chest showed the lungs clear, but the heart definitely enlarged to the left.

A *gastro-intestinal Roentgen* series reported definite herniation of the stomach mucosa about the size of a walnut through the oesophageal opening. It was otherwise entirely normal.

Vital capacity tests ranged from 2500-3000.

**COMMENT:** At first it was thought that this patient suffered from two distinct types of pain and discomfort; the first severe and paroxysmal in character, possibly due to angina pectoris, the second less severe, relieved by foods and alkalies, of longer duration, probably related to his hyperacidity and herniation.

Laboratory studies were thought to support these diagnoses. However, subsequent observation of this patient over a period of a year and a half has made the diagnosis of angina pectoris seem less likely. This seems to be true because of the lack of response to nitro-glycerine, and be-



Fig. 4. Case VII.

cause exertion does not produce the attacks of pain but indeed he insists sometimes it actually relieves them. In view of these facts it is difficult to decide whether or not any of this patient's severe pain was due to heart disease or whether it was due to temporary incarceration of the herniated stomach. If anginal in character, may it not have been produced in an already diseased heart by reflex disturbance from the protrusion of the stomach into the chest cavity?

**Case 7.**—E. C. Aged 36. American. Housewife. This patient entered the hospital for the draining of a small abscess in the breast. In the course of routine study her urine was found to be strongly positive for sugar and her blood sugar contained 444 mg. of glucose per 100 c.c. (not fasting). She was placed upon a diabetic regime and improved until she was discharged with a fasting blood sugar of 190 mg. While in the hospital she was discovered to have a blood tinged mucous vaginal discharge. Pelvic examination resulted in a diagnosis of carcinoma of the fundus and treatment by radium was recommended. This was done and she continued to have deep x-ray therapy from that time to the present. Four years later she re-entered the clinic because she felt tired and because she had been having "indigestion." This consisted of attacks of mild vomiting or regurgitation of a few mouthfuls of dark colored liquid. They were not associated with pain or nausea and were never severe. They almost always came on in the morning, after a good night's sleep. There was also dull pain across the lower back. Otherwise history was unimportant.

**PHYSICAL EXAMINATION** showed a woman with pale skin which was loose, flabby, suggesting recent weight loss. Her lungs were clear throughout. Her heart was normal in size to percussion, the rhythm was regular, rate 90, sounds of good quality, no murmurs were heard. Blood pressure was 134/70. The abdomen was relaxed and flabby and there was slight tenderness in both lower quadrants. Knee jerks were active, extremities showed marked varicosities.

Laboratory studies reported blood sugar varying from 246 to 222, with sugar in her urine, but no acetone or dia-



Fig. 5. Case VIII.

etic acid. There was also a small amount of albumin, no casts or red cells.

Blood serology was positive.

Hemoglobin was 84 per cent. Red Cells were 4,490,000; white cells 7,100.

Blood sedimentation rate was 19 millimeters in one hour.

A *gastro-intestinal Roentgen* series revealed a moderate sized hernia through the oesophageal opening, demonstrable only in the recumbent position. There was no sign of malignancy nor any other organic lesion.

COMMENT: In view of the patient's diagnosis of malignancy four years before the onset of her gastro-intestinal symptoms, it was at first feared that these might be due to metastatic lesions from her original growth. The presence of the hernia demonstrated by roentgenogram, however, seemed to account for her gastro-intestinal symptoms.

Case 8.—P. O. Aged 74. American. Stableman. This patient was admitted complaining of epigastric distress and vomiting. He was well until five years before when during his meal or immediately afterward he began to have a slight distressed feeling in his epigastrium followed by vomiting. These symptoms did not trouble him much at first, but in the year previous to admission they had become progressively worse, so that he then had almost daily vomiting: He described this by saying, that a few minutes after beginning his meal he would have a sudden return to his mouth of food just eaten; he would vomit this out, then return to the table and finish his meal in comfort. There was no nausea at all, and no pain—only a vague sense of discomfort. The food came up in a rush, and consisted only of that eaten a few minutes before. In addition he stated that at other times the food seemed to stick in his throat and "did not want to go all the way down." There was no loss of weight. There were no other gastro-intestinal symptoms and no symptoms referable to any other system.

PHYSICAL EXAMINATION showed a rather healthy looking old man with no evidence of recent loss of weight. The lungs were entirely clear. The heart to percussion was slightly enlarged to the left; there were frequent extra

systoles; the rate was normal; the sounds were of good quality and there were no murmurs. Blood pressure was 120/80. Examination of the abdomen was entirely negative. Deep reflexes were normal.

Urinalyses were negative.

Blood serology was negative.

Blood count showed hemoglobin being 95 Per cent, red cells 6,000,000 and white cells 11,000.

Stool examinations were negative for occult blood.

The Graham Test done twice with the double oral method, showed no filling.

A *gastro-intestinal Roentgen* series showed a hernia the size of an apple through the hiatus opening. It was otherwise entirely negative.

Non-protein nitrogen was 30 mg. per 100 cc.

COMMENT: Although, the Graham Test showed no filling, his symptoms were not thought to suggest gall-bladder disease.

Case 9.—H. D. Aged 62. Irish. Housewife. This patient for the past twenty-five years had been troubled with attacks of vomiting which came on almost immediately after eating. These were accompanied by a sense of discomfort in the epigastrium, but by no actual pain. There were eructations of gas. The vomiting came on without nausea and without warning. There was no relation of the attacks to meals and no relief by eating food. Before admission the attacks had been so severe as to make her consult a physician, who sent her to the hospital for study and treatment. In the hospital she was placed on a soft diet and advised to see a surgeon immediately. After leaving the hospital she continued on a soft diet, and felt greatly improved, being without distress or vomiting. She stated that she had gained 8 pounds in the previous months. There were no other symptoms referable to any other system.

PHYSICAL EXAMINATION revealed a well nourished Irish woman with good spirits. Lungs were entirely clear. The heart was normal to percussion; the rate was 74; the rhythm regular; no murmurs were heard. Peripheral blood vessels showed moderate sclerosis and blood pressure

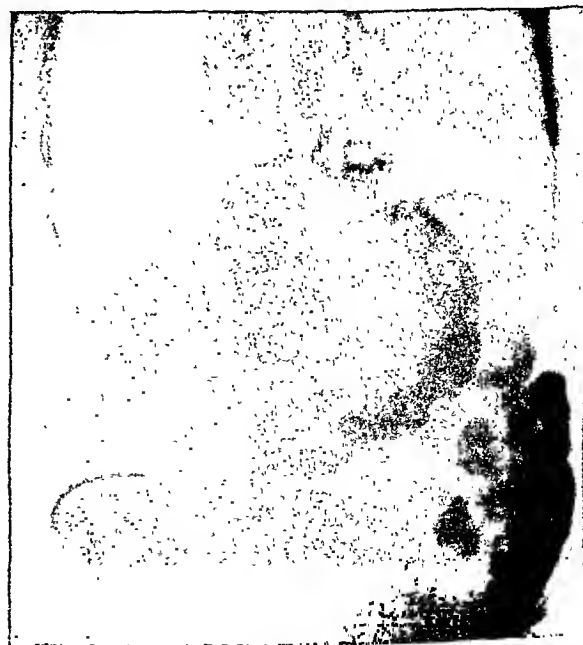


Fig. 6. Case IX.

was 170/105. There was very slight tenderness in the epigastrium, but otherwise the abdomen was negative. Varicosities were present in both lower legs; deep reflexes were normal.

Urinalyses were negative except on one occasion when a slight trace of albumin was found.

Laboratory studies showed a negative blood serology.

Blood count showed 93 per cent hemoglobin, 4,985,000 red cells, 9,700 white cells, with a normal differential count.

Stool examination showed no occult blood in the Ben-zidine test.

The *gastro-intestinal Roentgen* series revealed a herniation of the stomach about the size of an apple through the oesophageal hiatus, in which mucosal folds could be easily traced. This hernia was seen only with the patient in a recumbent position, since in the upright position no hernia could be demonstrated.

COMMENT: It is interesting that the patient was so completely relieved of symptoms by small, frequent meals of soft food. One notes too the need to examine these patients in recumbent as well as in upright positions.

*Case 10.*—M. R. Aged 47. Irish. Housewife. This patient, five years before admission, in the middle of the night, was seized with severe knife-like pain in the left chest and in the epigastrium, which radiated through to the mid back. Pain lasted for several hours. It was associated with much nausea and vomiting. The vomitus contained only the food eaten the night before, and none from the preceding meal. This attack gradually subsided under the care of a local physician and although there was an occasional dull ache in the area described, she had no further attacks until two years ago. In this second attack she again had severe pain and vomiting and a priest was called to anoint her, as she thought she was going to die. She then remained free from pain and vomiting until about two weeks before admission to the clinic. Since that time she has had occasionally sharp intermittent, cramp-like pain in the left lower chest. This was associated with some eructations of gas, but it had no relation to food and

was not relieved by food. About two years before she first noticed slight difficulty in swallowing solid food, and also even in swallowing liquids at times. There had been no significant weight loss and the rest of the history was unimportant, except for a history of increased dyspnea, brought on by exertion or excitement, and of some oedema of the ankles in the evening.

PHYSICAL EXAMINATION revealed a small, under-nourished woman with rather marked pallor of the mucous membranes and an icteroid tinge to the skin. The heart measurements were normal, the rate was 80, the rhythm was regular, the sounds were of good quality; however, there was a loud systolic murmur heard over the entire cardiac area, but heard best at the pulmonic area. No diastolic murmur was heard. Blood pressure was 100/60. The lungs and abdomen were entirely negative to examination. Pelvic examination showed a firm mass, thought to be intramural myoma. There was also felt an enlarged slightly tender mass in the region of the left ovary.

Urinalyses were normal.

Wassermann test was negative.

Blood studies were interesting since they showed a severe grade of anaemia, the hemoglobin by Sahli method being 30 per cent, the red cells 3,320,000, and the white cells 6,700. Differential count was normal. Reticulocyte count was 1%. The average red cell diameter was 7.18 microns.

Stool examinations on meat free diet were negative for blood.

A gastric analysis done with histamine, showed no free acid in any specimen.

Blood sedimentation rate was 14 millimeters in one hour.

Radiographic examination of the gastro-intestinal tract was entirely normal except for small herniation of the stomach through the oesophageal opening.

Graham Test was entirely normal.

COMMENT: This patient's story might well suggest the presence of gall-stones. A temporary incarceration of the hernia is thought to explain her attacks of severe pain.

## REFERENCES

1. Paré, Ambrose: *Opera Chirurgica* ab Ambrose Parco, Frankfurt 1610, ch. 30, p. 230.
2. Hildanus, Fabricius: *Opera Gulielmi Hildani*, Frankfurt 1646: een 2: obs. 33, p. 108.
3. Riverius, Lazari: *Opera Medica Universa*, London, 1698, obs. Cent quart. ob. 67.
4. Morgagni: *Seats and Causes of Diseases*, Vol. III, Letter 54, 1769.
5. Cooper, Sir Astley: *Treatise on Hernia*, London, 1824.
6. Bowditch, H. I.: *Treatise on Diaphragmatic Hernia*, Jewett Thomas & Co., Buffalo, 1853.
7. Andrew: The Height of the Diaphragm in Relation to the Position of Certain Abdominal Viscera. *Lancet*, I, 790, 1903.
8. Folkenord: Phrenic neurectomy as treatment of diaphragmatic hernia. *Acta med. Scandinavica*. 72:511-526, 1929.
9. Kienboech, R.: Über Megenschwüre bei Hernia und Eventratio Diaphragmatica. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 21:322, 1913-1914.
10. MacMillan, A. S.: Diaphragmatic Hernia. *Am. J. Roentgenol.* 7:143, 1920.
11. Rendick, R. A.: The Radiographic Examination of the Alimentary Tract with Analysis of Routine Examinations of 5033 Hospital Cases. *J. Radiol.* 5:124, 1924.
12. Morrison, L. B.: Diaphragmatic hernia of fundus of the stomach through the oesophageal hiatus. *J.A.M.A.*, 84:161-163 (Jan.) 1925.
13. Panceast, H. K.: and Bokes, R. E.: Non-traumatic left diaphragmatic hernia. *Arch. Int. Med.* 38:633-646 (Nov.) 1926.
14. Akerlund, A., Ochsall, H., and Key, E.: Hernia diaphragmatica Hiatus Oesophagel. "Der Hiatusbruch". *Acta. Radiol.* (Stockholm) 6, 3, 1926.
15. Ritvo, M.: Diaphragmatic hernia. *J.A.M.A.* 91:15-21 Jan. 4, 1930.
16. Harrington, S. W.: Symptoms and surgical treatment in 60 cases. *J.A.M.A.* 101:987-994, Sept. 23, 1933.
17. Hedblom, C.: Diaphragmatic Hernia. *J.A.M.A.*, 85:917, 1925.
18. Schatzki, R.: Die Beweglichkeit von Oesophagus und Magen innerhalb des Zwerchschlitzes beim alten Menschen *Fortsch. a. d. Geb. d. Roentgenstr.* 45:177, 1932.
19. Le Wald L. T.: Thoracic Stomach: *Radiology* 3: 91-102 (Aug.) 1921.
20. Richards, L. G.: Non-traumatic hernia of the diaphragm. *Am. Jour. Otol., Rhinol. and Laryng.* 32:1146-1168, 1923.
21. Morrison, L. B., Morrison, S. L., and Delaney, J. H.: Herniation of the fundus of the stomach through the esophageal hiatus. *N. E. J. Med.* 210, 624-632, Mar. 22, 1934.
22. Healy, T. R.: Symptoms observed in 53 cases of non-traumatic diaphragmatic hernia. *Am. J. Roentgenol.* 13:266-271 (Jan.) 1925.
23. Eppinger, H.: Allg. und spez. Pathologie des Zwerchfells. Suppl. zu Nothnagel, Spez. Pathol. und Therapie. Holder, Wien und Leipzig, 1911.
24. Wagner, A.: Esophageal orifice hernias. *Acta. Radiol.* 13:466-482, 1933.
25. Truesdale, P. E.: Symptoms and physical signs with a report of 12 cases treated by operation. *Am. J. Surg.* 94:528-538 (Oct.) 1931.
26. Key, E.: Fall von Hernia diaphragmatica, kompliziert mit penetrierendem Magengeschwür. *Zentralbl. F. Chirurg.*, 95, 1924.
27. Harrington, S. W.: Diaphragmatic hernia associated with traumatic gastric erosion and ulcer. *S.G.O.* 51:504-521 (Oct.) 1930.
28. Kroon, M.: Hernia of Oesophageal Hiatus combined with Gastric Ulcer and fatal Hemorrhage. *Svenska Lakertidningen*, 1067-1072, Sept. 13, 1929.
29. Gardner, K. D.: Diaphragmatic hernia associated with secondary anemia. *Am. J. M. Sc.*, 185:561, 1933.
30. Bock, A. V., Duliz, J. W. and Brooke, P. A.: Diaphragmatic hernia and secondary anemia. *N. E. J. Med.* 209:615-625, Sept. 28, 1933.
31. Harrington, S. W.: Diaphragmatic hernia. *Proc. of Staff Meet. Mayo Clin.* 3:241, 1928.
32. Harrington, S. W.: Phrenicotomy with diaphragmatic hernia. *Arch. Surg.* 18:561, 1929.
33. Goetze, O.: Die effektive Blockade des Nervus phrenicus. *Arch. F. Klin. Chirurg.*, 34:595, 1925.
34. Lemois, W. S.: The Physiological Effect of Phrenic Neurectomy *Arch. Surg.* 14: 2, 345, 1927.
35. Truesdale, P. E.: Hernia of the diaphragm—oesophageal type in adults. *N. E. J. Med.* 210:781-783, (April 2), 1934.

## SECTION VI—*Abdominal Surgery*

### The Use of Metal Clips in Gastrointestinal Anastomosis\* An Experimental Study

By

RALPH B. BETTMAN, M.D.†

and

LEO M. ZIMMERMAN, M.D.‡

CHICAGO, ILLINOIS

THE ease and rapidity with which metal skin clips may be applied in the closure of skin incisions has suggested the possibility of finding a similar method for approximating the stomach and bowel. E. Wyllys Andrews, (1), in 1911, reported the use of modified skin clips in the inner row of intestinal anastomoses in clinical surgery. He added that "in the lumen of the bowel these need not be absorbable, as they fall into the canal later." The problem has received scant consideration since these pioneer observations were made.

In our approach to the question, we wished to determine whether a single row of Michel skin clips applied to the mucosal surfaces might not adequately approximate the edges of the stomach or bowel for the formation of gastrointestinal anastomoses. With this method we hoped that broad serosal coaptation could be obtained, the clips on the inner surface would probably slough out and be discharged, the permanent burying of foreign suture substances would be avoided and the formation of a flange or shelf would be minimized. We were interested specifically in determining the feasibility and safety of the method, whether it permitted saving in time and operative work, if adequate hemostasis could be secured, what the immediate post-operative course would be, the subsequent fate of the clips, the reaction of the tissues and the gross and microscopic healing at the line of anastomosis.

#### EXPERIMENTAL METHODS

In order to answer these questions, we performed a series of gastroenterostomies and of partial gastric resections in a number of dogs. The operations were done under ether or intravenous nembutal anesthesia, with the usual aseptic precautions. Because of the length and mobility of the duodenum, this portion of the gut, rather than the jejunum, was usually used for anastomosis with the stomach. In most of the operations, the loops to be anastomosed were approximated and incised in the usual manner, and the clips

placed first on the posterior limb of the stoma. After rounding the "corners", the portion already closed was depressed and the edges to be united were everted to permit the placing of further clips. The last 2 or 3 cms. of the stoma could not, of course, be closed in this fashion. In some of the animals an interrupted suture or two was used; in others, clips were placed on the serosal surface, turning in the cut edges. In the latter, no attempt was made to bury the clips. In another group of animals, a gastrotomy incision was made on the anterior wall of the stomach, and through this incision the anastomosis between bowel and posterior stomach wall was effected from within the stomach cavity. In some instances, an oval window was cut in the posterior wall of the stomach to provide a circular stoma instead of the usual slit-like opening. This technique permitted more accurate apposition of the edges to be united and minimized the flange at the site of anastomosis. The gastrotomy incisions were closed either by suture or by a row of clips placed on the serosal surfaces, inverting the cut edges. The abdominal wounds were closed in layers and the animals were returned to their cages. Water by mouth was permitted on the day of operation, and food as soon thereafter as desired by the animal. A diet of kitchen scraps was maintained for the duration of the experiment. The animals were sacrificed and post-mortem examinations made at intervals ranging from three days to six months.

#### RESULTS

It was soon found that, in the dog, it was feasible to perform gastrointestinal anastomoses by the use of a single row of Michel clips applied in the manner described. After the first few attempts, the mortality in simple gastroenterostomy was practically nil, although it was material in the gastric resections. However, a parallel series of experiments, in which a single row of catgut sutures was used instead of the clips gave a practically identical mortality rate. This seemed to indicate that whenever the total gastric content was forced to leave the stomach through the artificial stoma, the danger of the operation was greatly increased, regardless of whether clips or sutures were used. Death from hemorrhage was not observed in

\*From the Nelson Morris Institute of Research of the Michael Reese Hospital.

†Associate Professor of Clinical Surgery—Rush Medical College.

‡Associate in Surgery—Northwestern University Medical School.

Submitted April 22, 1937.



Fig. 1

any of the experiments. While recognizing the fact that the danger of hemorrhage in the dog is in no way comparable with that in man, the total absence of demonstrable postoperative bleeding in our animals indicated that hemorrhage from the cut edges was adequately controlled by the clip technique. On several occasions, when a larger blood vessel was severed, bleeding was promptly stopped by placing a clip over the spurting vessel. The operative time and effort were strikingly reduced by the clip method. The immediate convalescence, as a rule, was excellent. The animals were alert and active within a very few days, ate freely of a mixed diet, and remained well-fed and in good condition until they were sacrificed.

When this work was begun, we anticipated that the clips placed on the mucosal surfaces would quickly become loosened and fall into the lumen of the bowel. We were rather surprised to find, at reoperation or autopsy at varying intervals after the operation, that many of the clips were retained, and that frequently they were imbedded in the tissues. The persisting clips seemed to be very well tolerated and gave rise to no ulceration or marked inflammatory reaction. The stomata remained patulous and apparently functioned well. In fact, it seemed to us that in some specimens the stomata were held open by the ring of clips. It is entirely possible that this persistently patent circular stoma might have definite advantages over the usual potential, slit-like one resulting from suture anastomoses.

In the animals sacrificed at varying periods following operation, the peritoneum was found to be smooth and free, with a minimum of adhesions about the anastomosis. Even in those instances in which the last portion of the anastomosis was closed with clips placed on the serosal surfaces, there were relatively few adhesions. As can be seen in the photographs, the healing, both at the serosal and the mucosal surfaces was strikingly smooth. Microscopically, after

Fig. 1. Serosal surface at site of gastrointestinal anastomosis showing freedom of scar tissue.

healing had occurred, the mucosa of the stomach passed over into that of the duodenum, without interruption. A minute, scarcely detectable wedge of scar tissue, alone, marked the site of anastomosis. Nowhere was there evidence of inflammation or infiltration. Even about the retained clips, there was very little evidence of foreign body reaction.

#### SUMMARY

Summarizing our results, the experiments thus far have shown that, in the dog, gastrointestinal anastomoses can be made with a single row of metal clips placed on the lumen side of the structures to be united. The operation is very quickly done, with little operative trauma. Bleeding is easily controlled; convalescence is rapid, and the condition of the animals remains good. Many of the clips, instead of being extruded, as had been anticipated, remain in place and become firmly imbedded in the tissues. Gross and microscopic healing is very satisfactory, with a minimum of adhesion and inflammatory reaction at the site of anastomosis.

#### EXPERIMENTS WITH ABSORBABLE METAL CLIPS

Believing that the retention of the clips might be objectionable in provoking irritation or ulceration, an attempt was made to find an absorbable substitute for the Michel clip. Search for absorbable metal suture materials has been made from time to time by several investigators. In 1878, Dr. E. C. Huse, (3), an American, recommended magnesium ligatures, stating that he had used them three times. E. W. Andrews, (2), working in this laboratory some 20 years ago, studied the absorbability, flexibility and tensile strength of various metals and their alloys, hoping to be able to



Fig. 2

Fig. 2. Duodenum opened showing stoma of duodeno-gastrostomy. Stoma is held open by ring of clips.



Fig. 3

use them for deep sutures and ligatures. His search for an absorbable metal sufficiently flexible for these purposes was unsuccessful. Seelig (4) studied the properties of commercial metallic magnesium with the same end in view, but found it too brittle. He succeeded, however, in securing chemically pure magnesium wire which was sufficiently strong and pliable to serve as suture material. Such sutures absorbed readily and were tolerated remarkably well both locally and systemically. Unfortunately, in the process of absorption, oxidation of the magnesium occurred, with the liberation of hydrogen gas, which absorbed at a rate somewhat slower than it was formed. The resultant gas cysts separated the tissues at the line of suture, and were considered of sufficient significance to prohibit the employment of magnesium sutures in surgery.

We felt that this objection would not maintain if the magnesium were used in the form of clips applied within the lumen of the bowel, since, with such application, only the point of the prong is buried. At this point we wish to express our appreciation of the very generous assistance rendered us by the American Magnesium Corporation, which provided us, without expense, with ribbons of pure metallic magnesium of suitable width, thickness and flexibility for making into clips. It was soon found that exact reproductions of the Michel type clip could not be made of this material, because even the softer grades of the metal were too brittle to permit the punching out of prongs. However, a satisfactory substitute was found in a simple curved band sharpened at both ends, and having the general shape and size of the Michel clip. These were sufficiently flexible for use in our experiments, although much more care was required in placing the clips, since, if compressed too tightly, they tended to break in the middle. Properly applied, their tensile strength and elasticity were sufficient to hold the anastomosed structures in apposition.

With these clips we performed a series of experiments similar to those described with the German silver clips and with similar results so far as mortality, convalescence and control of hemorrhage were concerned. The clips were found to absorb with striking rapidity. Wounds inspected after 3 or 4 days revealed extensive, irregular corrosion of the clips, sufficiently advanced to break some of them. After 7 days only fragments of clips were left, and these vestiges disappeared between the 10th and 14th days. Clips placed on the serosal surfaces were absorbed at a much slower rate than those within the lumen of stomach or

Fig. 3. Cross section at site of gastro-duodenal anastomosis.

bowel. Gas cysts were noted occasionally about retained prongs of magnesium, varying from minute size to 4 or 5 mm. in diameter. They were much more evident about clips placed on the serosal surfaces. No untoward effect could be ascribed to these small gasous accumulations about clip ends.

Healing was very satisfactory in these experiments. Seelig, in the studies mentioned before, was impressed with the absence of leucocytic infiltration or other evidence of reaction to buried magnesium. We were able to confirm this observation. Nor were there systemic effects which could be attributed to the magnesium. The fragility of the clips, and their rapid absorbability, however, were construed as possible sources of danger. In other respects, the absorbable clips seemed to adequately fulfil their purpose in the experiments.

### GENERAL SUMMARY

Gastroenterostomy and enteroenterostomy can be safely performed in dogs by using a single row of German silver Michel clips placed on the mucosal surfaces of the structures forming the stoma. This method greatly reduces the time and operative work required. Bleeding can be adequately controlled, and the post-operative convalescence is rapid and uneventful. Healing is very satisfactory, with a minimum of reaction and scar formation. These non-absorbable clips, instead of being sloughed into the lumen of the bowel, tend to become imbedded. This retention of metallic foreign bodies is theoretically objectionable, although no injurious effects were seen in the experimental animals. On the other hand, the ring of clips served



Fig. 4

Fig. 4. Microscopic section of site of gastrointestinal anastomosis.



to hold the stomata open. From the standpoint of function, such a patulous opening might have real advantages over the potential, slit-like stoma of usual suture anastomoses.

Absorbable metal clips made of pure metallic magnesium may be used with apparently the same degree of effectiveness and safety. These clips are more fragile, and therefore, somewhat more difficult to apply.

They are rapidly absorbed within the gastric or intestinal lumen, and obviate the theoretical objection of retained metallic bodies at the line of anastomosis. On the other hand, the early dissolution and fragmentation of the clips may constitute an additional hazard.

This work is purely experimental in character, and no attempt has been made to apply it clinically.

#### REFERENCES

1. Andrews, E. Wylls: New Mechanical Devices for Closure of Wounds. *J.A.M.A.*, 57:602, 1911.
2. Andrews, E. Wylls: Absorbable Metal Clips as Substitute for Ligatures and Deep Sutures in Wound Closure. *J.A.M.A.*, 69:278, 1917.
3. Huse, E. C.: Quoted by Seelig.
4. Seelig, M. G.: A Study of Magnesium Wire as an Absorbable Suture and Ligature Material. *Arch. Surg.*, 8:669, 1924.

## ABSTRACTS

FRANK L. MELENEY, M.D., New York, New York.

"Zinc Peroxide in the Treatment of Microaerophilic and Anaerobic Infections." *Ann. Surg.*, Vol. 101, No. 4, April, 1935.

The author presents case histories of six patients who had chronic, ulcerative, burrowing, non-gangrenous lesions of the abdominal wall apparently due to a "micro-aerophilic hemolytic streptococcus." Three of these patients were treated locally with zinc peroxide, with remarkable responses.

The organism obtained from these wounds and sinuses was a streptococcus which had anerobic tendencies but which was not a true anerobe, however, for on subsequent artificial cultivations, it gradually became more and more capable of growing aerobically. They therefore classified it as a "micro-aerophilic hemolytic streptococcus." Vaccines and Besredka filtrates made from this organism did not yield good results and improvement was always followed by discouraging retrogression.

The preference of the organism for an anerobic environment suggested the use of a peroxide to inhibit its activity. Zinc peroxide was used because of its ability to yield oxygen over a relatively long period of time rather than give it off abruptly.

A creamy suspension was made with zinc peroxide in sterile water or with gelatine or as in one case, with a 5 per cent pyrophosphate solution which suspends the heavy powder better than gelatine and does not favor the growth of other organisms. This suspension was then applied to the ulcerative surface of the wounds and injected deep into the sinuses with the result that in a few days when cultures were made of these wounds, the microaerophilic hemolytic streptococcus was no longer found, but in its place was a green aerobic streptococcus. This occurred in two of the three cases treated with zinc peroxide and the author is of the opinion that the original organism had become changed or dissociated in the wound following the use of the zinc peroxide. Following this treatment the patients felt better, their fever subsided and the wounds began to heal. The rolled in margins were trimmed away and soon it was possible to plant some skin grafts which in each case grew nicely and fused and the wound soon completely healed.

The author states that in his search of the literature he was unable to find any adequate description of this disease which he states begins gradually and is characterized by the following course. What appears to be an ordinary drainage tract from a deep or subcutaneous abscess fails to follow the usual course of healing. Improvement which may have been present in early stages of the injection gradually ceases. The skin margins become undermined with liquefaction of the subcutaneous fat and connective

tissue. There is no gangrene of the skin but the edges roll in. The undermining progresses and the skin opens widely, exposing a base of gelatinous, pale granulation tissue. In one or more places, in the neighborhood of the lesion, the skin will take on a dull red, or bluish appearance. It is then found that the undermining has extended beneath this area and the skin has become thinned out as if it were being liquefied from beneath. After a number of weeks a small opening appears in this thin area. This secondary opening gradually enlarges and the margin may extend until it fuses with the original ulcer. In lower abdominal lesions the undermining frequently spreads down toward the groin or toward the pubic region, extending into the vulva, or into the scrotum, or beneath the crease of the groin into the thigh. In these regions it may extend inward, dissecting beneath the muscles and forming deep sinuses into the pelvis.

The lesion is usually only moderately painful but the pain may be excruciating. Fever develops daily with temperature rises to 101 and 103.

After months or years of suppuration the lesion may gradually heal spontaneously, or burrow deep and produce death either by erosion into a large vessel or by the gradual development of amyloid degeneration of the liver, spleen and kidneys.

Although this disease is relatively rare, the author notes that its chromacity and its severity are indicative of its importance.

Charles T. Sturgeon, Los Angeles.

BALFOUR, D. C.

*Principles of Gastric Surgery. Surgery, Gynecology and Obstetrics, Vol. 60, No. 2A, February, 1935, pp. 257-263.*

In the Murphy Memorial lecture for 1934 the author reviews the history of gastric surgery and shows that it is based on a foundation of physiological knowledge, exact pathological classification of lesions, accuracy of diagnosis, better understanding of the indications for operation, more intelligent application of operative procedures, and established principles of technique. He laments the fact that in only one out of four cases of cancer of the stomach can resection be attempted, when first seen by the surgeon. If resection cannot be done, the exclusion operation of Devine should be performed. Gastroenterostomy has a small place in the treatment of gastric cancer; should marked or prolonged improvement follow this operation it would constitute evidence that the growth could have been removed.

The most effective treatment, both in respect to maintaining low mortality and low morbidity, and increasing curability depends on the following factors: first, pre-operative overcoming of the effects of dehydration; second,

pre-operative cleansing of the stomach by lavage; third, anaesthesia adequate to allow satisfactory examination of the growth, and possible detection of metastases; fourth, wide removal of the growth and a segment of the duodenum, together with as nearly complete as possible extirpation of lymph nodes; and last, such restoration of gastrointestinal continuity that the anastomosis not only will function well, but in the event of recurrence it will most likely ensure protection against obstruction of the gastro-intestinal tract. The chief problem concerning ulcers, which still awaits solution, concerns the cause. The management of duodenal ulcer, and the indications for operation, are relatively well understood and generally practiced. Concerning gastric ulcer there is no such harmony of opinion. That an apparently benign gastric ulcer may undergo malignant change is generally agreed, but the frequency with which such a change takes place is a subject of considerable difference of opinion. Should some method become available to distinguish clinically these lesions the benign ulcer could be treated medically without the ever present fear and humiliation of attempting to cure a malignant lesion by diet and alkalies.

The dictum that if the gastric ulcer does not yield promptly to medical treatment it should be classed as a lesion other than ulcer, should be adhered to strictly.

Nelson M. Percy, Chicago.

MOSHER, H. P.

*The Esophagus. Surgery, Gynecology and Obstetrics, Vol. 60, No. 2A, February 15, 1935, pp. 402-417.*

The author reviews the work done on the esophagus in Boston, and gives the Boston point of view.

Webbs of the esophagus occur usually in the upper part, and are very frequently associated with the exostosis of the cervical vertebrae. The treatment of such conditions is to excise a portion of them, and to periodically dilate the esophagus by means of bougies.

Pouches in the esophageal wall at the level of the bifurcation of the trachea are not uncommon. They are due to a healing of a suppurating tuberculous gland which attaches itself to the esophagus.

The author believes that pouches at the upper end of the esophagus are embryological in origin, and should be treated by the two stage external operation.

Strictures resulting from the swallowing of caustics are treated by appropriate bougienage.

The author discusses no foreign body found in the esophagus other than the open safety pin with the point upward. If the pin cannot be closed with any one of the several safety pin closers on the market, it should be pushed into the stomach and watched by X-ray at frequent intervals. The pin may remain in the stomach straddling the pylorus. In such a case the pin must be removed surgically. In most cases the pin leaves the stomach promptly, and, within a week is recovered from the bed pan.

The author professes a sort of helplessness about carcinoma of the esophagus. He has seen some good results from massive doses of X-ray, and is hopeful that surgery will soon have more to offer.

A few patients with the Plummer Vincent syndrome have been seen by the author. That syndrome connotes secondary anemia with a history of long standing dysphagia and a smooth tongue. The treatment is appropriate bougienage. Ulcer of the esophagus is rare in the author's experience. He believes that it should occur in the lower part of the esophagus, and can be diagnosed best by X-ray.

Congenital shortening of the esophagus occurs rarely; shortening may result from the contraction of fibrous tissue following caustic burns. Septa may occur across the esophagus dividing it into several segments. Rupture and

dilatation of these septa must be done very carefully to avoid rupture of the esophagus.

It is the author's belief that in the condition called cardiospasm there is actually no spasm at all, but that there is a backward bend of the esophagus with a twisting and fibrosis of the esophageal wall at the crural canal.

During the course of acute and chronic infections, as well as during the course of infections in organs adjacent to the esophagus, marked involvement of the esophagus may occur. It seems then that fibrosis and subsequent stricture of the esophagus may occur at any point.

The author points out that esophagoscopy is not an entirely harmless procedure. It carries a mortality of 1.5 per cent.

Twenty-four figures accompany the article.

Nelson M. Percy, Chicago.

ABELL, I.

*The Diagnosis and Treatment of Diverticulitis and Diverticulosis. Surgery, Gynecology and Obstetrics, Vol. 60, No. 2A, February 15, 1935, pp. 370-377.*

Diverticula have been described as congenital or true, and acquired or false, the former containing all of the coats of the intestinal tract, the latter representing protrusions or herniations of the mucous and submucous coats through apertures in the muscularis. Diverticula may be found at all points in the intestinal tract from the pharyngo-esophageal junction to, and including, the rectum. They occur singly in the upper part of the digestive tube, while in the lower part, particularly the left half of the colon, they may be very numerous. They are found most frequently in middle aged men.

Pulsion diverticula of the esophagus are seen most frequently at the level of the lower border of the cricoid cartilage. The history of their development is characteristic. Their size and extent may be readily determined by fluoroscopic examination. Curative treatment consists in extirpation of the sac in a one-stage or two-stage operation followed by periodic dilations of the esophagus.

Diverticula of the lower end of the esophagus, when associated with cardiospasm, are best treated by treating the cardiospasm.

Diverticula may occur in any part of the duodenum. They are in the jejunum, and are found in the ileum usually as a Meckel's diverticulum. The retention and decomposition of food particles in a diverticulum will lead to distention, irritation and inflammation, which requires treatment. The diagnosis of diverticulitis in a typical or rare situations is usually made after X-ray examination, or at operation. If a single inflamed diverticulum is present, it should be excised. Diverticula are observed far more frequently in the colon than elsewhere in the intestinal tract. Autopsy records show the presence of diverticula in 5 per cent of all subjects over 40 years of age. They are most commonly found in the sigmoid and descending colon, while in 85 per cent of the cases the distribution of diverticula is throughout the entire colon. Occasionally diverticula are found in the appendix where they project from the lumen into the tissues of the meso-appendix.

Granting the presence of diverticulitis one of several results may follow: namely, resolution; perforation with resultant peritonitis and its sequelae; thickening of the gut wall, and its mesentery, so that obstruction of varying degrees results. Treatment during the acute stages, when the condition is understood, is medical, while treatment of the various complications is surgical. An obstructing mass which cannot be differentiated from carcinoma should be explored surgically and treated appropriately.

Nelson M. Percy, Chicago.

CHURCHILL, E. D.

*Esophageal Surgery. Surgery, Gynecology and Obstetrics, Vol. 60, No. 2A, February 15, 1935, pp. 417-423.*

In the author's experience with the surgical treatment of carcinoma of the lower end of the esophagus the procedure described by Sauerbruch was found thoroughly practical. By an extra pleural approach the diaphragmatic pleura is stripped off, and the diaphragm incised radially from the esophageal hiatus. The growth is mobilized and the stomach drawn upward through the diaphragm. The esophagus is severed from the cardiac end of the stomach and closed. The entire mass is now placed into the stomach by a modified Witzel procedure. This operation is satisfactory and not overly difficult, but as a one stage procedure it is too extensive. If the stomach is mobilized, and the absence of hepatic metastases determined at a previous laparotomy it would be much less extensive. The author proposes such modifications.

The construction of a new esophagus from the skin of the thorax by the method of Rovsing is a surgical feat that will certainly be of increasing use in the future. Although it was first described in the treatment of strictures, it may be used in the treatment of carcinoma also.

The author reports one case of mediastinal abscess which was drained successfully by an extra pleural posterior approach. In the treatment of intractable severe cardiospasm the author has employed esophagogastric anastomosis successfully in two cases.

Five figures and a bibliography accompany the article.  
Nelson M. Percy, Chicago.

FEY, A., AND CUBBINS, W. R.

*Acute Mechanical Intestinal Obstructions. Mortality with and without Enterostomies. S., G. and O., Vol. 60, No. 3, March, 1935, pp. 738-745.*

The authors present a study of 241 cases of "acute mechanical intestinal obstruction" from the files of the Cook County Hospital occurring between 1922 and 1931. Only those cases which were operated on have been studied. Cases of obstruction secondary to carcinoma, pelvic abscess, or strangulated external herniae are not included in this series.

Adhesions forming bands or kinks accounted for 74 per cent of the cases. Intussusception, internal herniae, and Meckel's diverticulum were causes in many cases. Certain other rarer conditions were also found.

The cardinal symptoms presented by these patients were pain, nausea, vomiting and constipation. Auscultation will show peristalsis to be most active at the height of the pain. Distention of the abdomen is not always present, nor is peristalsis always visible. The results of enemata are of little or no diagnostic value. Elevation of temperature, even in the presence of gangrenous bowel, is an uncommon finding. The pulse rate varies in direct proportion to the toxicity of the patient. The degree of leukocytosis is not a dependable guide as to the state of the bowel wall.

The mortality in this series is 42.7 per cent. In the few cases in which enterostomy was done and the obstruction relieved, the mortality was as high as in those cases in which resection and anastomosis for gangrene was done. It seems that resection and anastomosis is the procedure of choice in all but a very few cases.

Death results from damage to the bowel wall due to distention and strangulation. The exact manner in which death occurs is still in doubt, but the pertinent and essential facts are that it follows decreased viability of the bowel.

The authors conclude that enterostomy, drainage of the bowel, and gun barrel fistula have not reduced the mortality in this series of cases. The administration of isotonic salt solutions intravenously and hypodermically is a life saving measure in many of these cases.

Four tables and a bibliography accompany the article.  
Nelson M. Percy, Chicago.

COLLIN, E. N., AND JONES, T. E.

*Benign Stricture of the Intestine Due to Irradiation of Carcinoma of the Cervix. S., G. and O. Vol. LIX, No. 4, Oct., 1934, pp. 644-649.*

In a series of 422 cases of carcinoma of the cervix treated with adequate and proper doses of x-ray and radium radiation, the authors found six cases with benign stricture of the intestine. In five cases the stricture was in the sigmoid, too high to be seen on sigmoidoscopic examination, while in one case the stricture was in the ileum. On fluoroscopic examination the lesions resemble the infiltrating type of carcinoma but with an hour-glass deformity showing a gradual change from the normal to the abnormal gut. The lumen of the intestine usually has a conical shape on each side of the lesion. Microscopically the constricted portion of the bowel shows changes similar to those previously described as being due to the action of roentgen rays and radium on the gastrointestinal tract.

The authors believe that "irradiation stricture" of the intestine should be suspected in any woman who develops unusual abdominal symptoms, particularly if they simulate intestinal obstruction several months or even years subsequent to irradiation therapy for carcinoma of the cervix. Minute inquiry should be made concerning the immediate post-radiation sequelae. In all of the cases reported having sigmoid lesions there was a history of tenesmus with bloody and mucoid stools for three weeks or longer following the irradiation therapy.

Such a complication of irradiation therapy can be prevented by changing the position of the intestines in relation to the source of radiation during actual time of treatment. Unless the intestines are fixed by adhesions, or by existing inflammation, they may be made to move away from the source of radiation by changing the position of the patient. The authors recommended the Trendelenburg position.

The importance of recognizing these lesions lies in the fact that they might easily be attributed to metastatic carcinoma in which case a hopeless rather than a hopeful prognosis would be given. The authors feel that this rare complication of the well proved present day efficacious irradiation therapy should not constitute a retarding influence on such therapy since it is so successfully treated by surgical intervention.

Three figures accompany the article.

N. M. Percy, Chicago.

ROSSER, C.

*Diothane in Surgery of the Anal Canal. A Clinical Survey of One Hundred Cases. S., G. and O. Vol. LIX, No. 5, Nov., 1934, pp. 820-823.*

The author reports the results of a series of 100 cases operated upon for haemorrhoids, fissure or other minor lesions of the anal canal using Diothane infiltration alone, or in conjunction with low spinal anaesthesia. Diothane may be used as a lateral block anaesthesia alone, in which case the patient experiences a stinging sensation for a few minutes before anaesthesia is established, or it may be injected in the same manner, or less extensively after anaesthesia has been established.

The advantages of using Diothane are that the anaesthesia lasts for 48 to 72 hours, that sensation returns very gradually, and that the period of painful sphincter spasm following other anaesthetics is entirely avoided. The disadvantages are that there is a slightly greater tendency to tag formation post operatively, and the occasional formation of apparently sterile chemical abscesses. No constitutional reactions to the drug were noted. The author feels that further experience with the drug will establish a technique giving more uniform results.

N. M. Percy, Chicago.

## SECTION VIII—Editorial

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastroenterological Association is in no way responsible for editorial expressions.

### PASSAGE OF NATIVE PROTEINS THROUGH THE NORMAL GASTRO-INTESTINAL WALL

THE ingestion of protein foods would give us little concern were they simply broken down into their component amino acids and thus absorbed into the body-economy to play the important rôle which they do. It is known, however, that during protein digestion certain of the soluble albumins and globulins, particularly those which are consumed raw, will at times escape digestion and enter directly into the blood stream and there act as totally foreign substances to give rise to a group of allergic syndromes expressed in such *bizarre* manifestations as prurigo, urticaria, eczema, angioneurotic edema, asthma, and gastro-intestinal disturbances such as vomiting, diarrhea and colic. Some investigators have placed migraine, certain ocular disturbances, and even epilepsy in this category. It is conceivable also that the escape of undigested proteins through the gastro-intestinal wall and the passage of their higher degradation products might also give rise to serious vascular changes and kidney involvements. Prolonged excessive indulgence in protein foods might perhaps result also in a marked reduction in the functions of the proteolytic enzymes. The problem, therefore, of the passage of unchanged proteins through the normal gastro-intestinal wall is not one of purely academic interest but becomes of concern to all physicians.

Inspection of the literature shows how hard it has been to approach the problem experimentally. While there is sufficient evidence to warrant the assumption that unsplit antigens enter the blood stream directly from the gastro-intestinal tract, (1), (2), (3), (4), (5), (6) the majority of the investigators have concluded that such a passage becomes possible only when the permeability of the gastro-intestinal wall is increased by abnormal or pathological conditions (7), (8), (9), (10). Stasis, the excessive flooding of the intestines with protein foods, lessened activity of the digestive enzymes, altered conditions of the intestinal mucosa and an abnormal permeability of the intestinal wall in new-born and suckling infants have been described as possible contributory causes.

The problem recently has been attacked again by Ratner and Gruehl (11) who felt that inadequate consideration had been given to the possibility that proteins in a native state may pass through the normal intestinal wall during the course of normal digestion. After surveying the literature Ratner and Gruehl were inclined to doubt the commonly held view that it is only when abnormal or pathological conditions of the intestinal mucosa are present that unchanged proteins enter the blood stream. It seems that the earlier investigators failed to take into consideration, among other factors, the nature of the proteins which they used, the quantities which they administered, and the limitations of the methods employed to detect the presence of unchanged protein in the blood stream. Actu-

ally, the difficulties of detecting foreign proteins and antibodies by the precipitin method are considerable, not only because the material is so greatly diluted in the blood and urine, but because ingested foreign proteins absorbed through the intestinal tract leave the blood stream as a rule within a few hours, and disappear from the urine within 24 hours. In the earlier experiments small numbers of animals were generally used, and artificial factors, such as trauma, were often introduced.

In their experimental work which was done largely on guinea pigs, Ratner and Gruehl utilized the anaphylaxis test as the biological method of choice to determine whether native antigens entered the blood stream directly. Animals were sensitized by feeding to eliminate any traumatization of the intestinal wall. Cow's milk was given. Although this is foreign to the natural diet of the guinea pig, it is non-irritating, non-toxic and well tolerated by the animals. The experiments showed that at least 50% of a large series of animals could be sensitized through natural ingestion, and that the passage of the antigens would take place in adult as well as in new-born animals. Though a single small dose would occasionally sensitize, fairly large amounts were necessary to sensitize animals with any degree of regularity.

Using human subjects Ratner and Gruehl found evidence to indicate that proteins from foods such as cottonseed, which are foreign to the diet, and even milk can enter the circulation. This occurred in normal persons and allergic patients and in adults as well as children. These observations corroborate the findings of Schloss and his co-workers (12) who, using immunological methods, showed that ingested native proteins from milk, eggs and almond will enter the blood of normal young children. Walzer *et al.* (13) using the Prausnitz-Küstner test, found that 88% of the normal adults whom they studied showed the presence of proteins of egg and fish in the blood after the ingestion of these foods. Walzer particularly stressed the physiological nature of this passage and because of its frequent occurrence in the average person, he believed it to be a normal phenomenon.

In view of these now several times repeated observations, the question may well be raised why all persons do not get sensitized to proteins. Ratner and Gruehl offer the following explanation. The body is provided with certain defensive measures which tend to impede the entrance of proteins in an unchanged state into the blood stream and tissues. These measures include the impermeability of the intestinal mucosa, the digestive enzymes, specific antibodies, and the excretory functions of the kidneys. Denaturation of proteins by heat and other culinary processes also aids the body in this defense. When antigens enter in small amounts and at frequent intervals, as has been shown by Wells (14), Schloss (12) and Laroche (15) an immunity is established. On the other hand, if anti-

gens enter in particularly large amounts and at infrequent intervals, then the animal or man may become profoundly sensitized and the subsequent ingestion of even small amounts of antigen is likely to produce allergic manifestations, shock and even death. It is possible that the normal absorption of small amounts of unchanged proteins may serve the useful purpose of constantly maintaining the body in a state of immunization against the ingestion of too large an amount of these substances. When the defense mechanism fails to act and antigens enter the blood stream in large amounts disease-producing hypersensitiveness may result.

Bret Ratner, New York City.

Clinical Professor of Pediatrics and Lecturer in Immunology, New York Univ., College of Medicine.

#### REFERENCES

1. Rosenau, M. J., and Anderson, J. F.: A study of the cause of sudden death following the injection of horse serum. Feeding experiments. *Hyg. Lab. Bull. U. S. P. H. S.*, 29:67, 1906.
2. Van Alostyne, E. v. N.: The absorption of protein without digestion. *Arch. Int. Med.*, 12:372, 1913.
3. Ratner, B.: A possible causal factor of food allergy in certain infants. *Am. J. Dis. Child.*, 36:277, 1923.
4. Ratner, B.: Placental transmission of alimentary anaphylaxis. *Proc. Soc. Exp. Biol. and Med.*, 20:88, 1932.
5. Mills, C. A.; Dorst, S. E.; Mynchenberg, G., and Nakayama, J.: Absorption from the intestine and excretion through the kidney of an unaltered complex protein substance, tissue fibrinogen. *Am. J. Physiol.*, 63:484, 1923.
6. Hektoen, L.; Kanai, P. H., and Dragstedt, L. R.: A study of protein absorption from the digestive tract by the precipitin test, with especial reference to thyroglobulin. *J. A. M. A.*, 84:114, 1925.
7. Hamburger, F., and Sperk, B.: Biologische Untersuchungen über Eiweissresorption von Darm aus. *Wien. klin. Wochenschr.*, 17:641, 1904.
8. Hettwer, J. P., and Kriz, R. A.: Absorption of undigested protein from the alimentary tract as determined by the direct anaphylaxis test. *Am. J. Physiol.*, 73:539, 1925.  
Hettwer, J. P., and Kriz-Hettwer: Further observations on the absorption of undigested protein. *Am. J. Physiol.*, 78:136, 1926.
9. Besredka, A.: De l'anaphylaxie lactique. *Ann. Inst. Pasteur*, 23:166, 1919.
10. Bernard, L., and Paraf, J.: Accidents de la sérothérapie antituberculeuse par le sérum de Vallée. *Bull. Soc. d'études scient. sur la tuberc.*, 1:64, 1911.
11. Ratner, B., and Gruehl, H. L.: Passage of Native proteins through the normal gastro-intestinal wall. *J. Clin. Investigation*, 13:517, 1934.
12. Anderson, A. F., and Schloss, O. M.: Allergy to cow's milk in infants with nutritional disorders. *Am. J. Dis. Child.*, 26:451, 1923.  
DuBois, R. O.; Schloss, O. M., and Myers, C.: The development of cutaneous hypersensitiveness following the intestinal absorption of antigenic protein. *Proc. Soc. Exper. Biol. and Med.*, 23:176, 1925.  
Anderson, A. F.; Schloss, O. M., and Myers, C.: The intestinal absorption of antigenic protein by normal infants. *Ibid.*, 23:180, 1925.
13. Walzer, M.: Studies in absorption of undigested proteins in human beings. I. A simple direct method of studying the absorption of undigested protein. *J. Immunol.*, 14:143, 1927.  
Brunner, M., and Walzer, M.: Absorption of undigested proteins in human beings. The absorption of unaltered fish proteins in adults. *Arch. Int. Med.*, 42:172, 1928.  
Sussman, H.; Davidson, A., and Walzer, M.: Absorption of undigested proteins in human beings. III. The absorption of unaltered egg protein in adults. *Ibid.*, 42:409, 1928.
14. Wells, H. G.: Studies in the chemistry of anaphylaxis. III. Experiments with isolated proteins, especially those of the hen's egg. *J. Infect. Dis.*, 9:147, 1911.
15. Laroche, G.; Richet, Ch. fils, and Saint-Girons, F.: Anaphylaxie alimentaire lactée. *Compt. rend. Soc. Biol.*, 70:169, 1911. *Arch. de méd. expér.*, 23:643, 1911.  
Anaphylaxie et immunité alimentaires expérimentales à l'ovoalbumine. *Compt. rend. Soc. de Biol.*, 74:87, 1913.  
L'anaphylaxie alimentaire aux oeufs. *Arch. de méd. expér.*, 26:51, 1914.

#### BREVITY

THIS Journal endeavors to make its columns available to clinicians and investigators who have something valuable to present to its twenty thousand, monthly readers. Further, the Journal is making a determined effort to print submitted, worth-while manuscripts promptly.

Each issue of this publication contains in excess of 60,000 words of text, an unusually large volume of material in a monthly periodical. This generous allowance is made possible by the Journal's large page. However, even this issue-size has become too limited to take care of manuscripts according to our policy. In consequence, constantly a large number of excellent papers await allotment to future numbers.

Upon analyzing certain submitted manuscripts, one finds them, to put it mildly, extremely "wordy." Not alone do some authors attempt to cover too much ground but, in doing so, they are very generous with language. Too literally do certain authors interpret Carlyle's "Produce! Produce! Were it but the pitifulest, infinitesimal fraction of a product, produce it, in God's name!"

Reviews of literature, case histories, long tabulations, musings and deductions—all, to be sure, of vast interest to individual authors, even if not necessary or fascinating to the general, or even the special reader—demand a veritable tower (not infrequently "Babel" in character) of words and consume valuable page space, space costly to print and, we admit, jealously surrendered when a huge pile of manuscripts cries out for placement.

In order that the Journal's policy of prompt publication, high standard of text and sightliness of format be maintained, we urge upon those who contemplate submitting manuscripts, that, before sending them, they re-read them frequently with the object of eliminating every unnecessary word, sentence, tabulation, chart, illustration or literature-reference which adds nothing to originality, interest, medical progress or the sum total of the world's knowledge.

If each author consistently follows these suggestions, our pages will be able to carry more and varied types of manuscript, prompt publication will be possible, each article will "earn its space" and—a practical angle—writers will have to pay considerably less for reprints.

We are passing on these suggestions to the Members of the Editorial Council and the Publications' Committee with the hope that, when articles are appraised for acceptance or rejection, they will consider in their decisions the weight of *brevity* as well as the significance of clinical or scientific data.

F. S.



## SECTION IX—Book Reviews

(This section is open to contributions from any medical reader, whether a member of the Editorial Council or not).

*"Body Mechanics in the Study and Treatment of Disease,"* by J. E. Goldthwait, L. T. Brown, L. T. Swain and J. G. Kuhns.—J. P. Lippincott Co., Phila., 1934.

IT is interesting to see how a group of four orthopedic surgeons look upon chronic diseases of various kinds, including not only those of the muscles, bones and joints, but also those of the abdominal viscera, heart, lungs, blood, metabolism, nervous system, etc.

The authors stress the importance of body types and posture; the relation of the bones to each other and their proper alignment, especially in the spine, thorax and pelvis; the position and tone of the diaphragm and muscles of the belly wall. They show how the abdominal viscera are supported by the diaphragm above and how the flat chest pushes the upper abdominal organs down, and how the lax belly wall favors this.

They have done a useful service in emphasizing the importance of body build and good posture, not only in "orthopedic cases" as usually understood, but in any sort of chronic medical patients so that the spine, pelvis and joints of the leg and foot may bear the weight of the body easily and avoid strain, so that the thorax shall be large and deep enough to give plenty of room for the ventilation of the lungs, so that the abdominal organs are kept in good position, their blood supply not interfered with, and good function preserved.

Clear directions are given about treatment, muscle building, exercises, posture and braces which are well illustrated by sketches. A series of case reports is included, showing how good results were obtained in various types of cripple and visceral disturbances. In reading this book we should remember that it sums up the experience of men who have done excellent work in bringing back a large and difficult group of physically inferior persons to comparative health.

On the other hand we meet various opinions and theories scattered through the book, which well may be criticized. In order to stress the value of their orthopedic work the Authors say in the preface, "No one who has studied the work of the various hospital clinics can fail to be impressed with the relatively small number of patients suffering from chronic disease that are accepted for treatment or that are receiving benefit from the treatment given". This seems neither polite nor true when one recalls the countless multitudes of chronic patients treated in our medical outpatient departments and wards, and in the many special clinics for chronic diseases such as tuberculosis, nephritis, diabetes, diseases of the heart, gastro-intestinal disease, thyroid, metabolism, etc., etc.

The rôle of orthopedics seems exaggerated at times. In the preface the question is asked, "Is it not possible that much of that which concerns chronic medicine has to do with the imperfect functioning of sagged or "misplaced organs"? and the answer is given. "In the broader knowledge of the special structure of

the individual—and of the varying mechanics of the body the solution of the problem of chronic disease is largely to be found."

Orthopedic treatment holds a large and honorable place in medicine, but it does not play the *major* part in "most chronic diseases". It seems possible after all that "the chronic patient" who is continually referred to throughout the book must be one of the comparatively limited group who go to the orthopedic surgeon and not "the chronic patient" of a general medical clinic.

We will quote a few examples of questionable opinions and theories in the field of diseases of the digestive organs. The right shoulder pain in gall-bladder disease is explained by the drag on the vagus nerve by the low diaphragm. No figures are given to show that this pain is more common or found only in gall-bladder cases with ptosis. Again, "Since passive congestion and chronic irritation are two of the factors which may lead to cancer, the potentialities of faulty Body Mechanics in the abdomen are serious when it is realized how commonly malignant disease is found there." No figures are given showing any relation between ptosis and abdominal cancer.

Again, "The pancreas is subject to pressure by the stomach and coeliac axis. Its internal secretion may be deranged, and lead to chronic glycosuria, ptosis being the original cause of such dysfunction." Some statistics to prove the frequency of glycosuria in ptosis would be welcome but none are given and it seems contrary to clinical experience.

Again, "The stomach should be above the navel". They seem ignorant of the work of Moody, Van Nuyss and Chamberlain, who showed clearly ten years ago that in 80% of 600 normal healthy adults the stomach reached 1 to 3 inches below the inter-iliac line. Finally there is the question of cause and effect. Do we not often find that the abdominal organs sag because the person is slender, weak and delicate, and not always that the person became weak, thin and sickly because his organs "sagged"?

It is a stimulating and interesting book and many medical problems are studied from a new point of view, but it would be more convincing in parts if these *Authors* did not ride their hobby so vigorously, and if new and striking theories had some statistics to back them up.

The book work is excellent and the illustrations clear and well chosen.

Franklin W. White, Boston.

*Methods of Treatment*, 5th Edition; by Logan Clendening, M.D., illustrated; Published by the C. V. Mosby Co., St. Louis, Mo., 1935. Price \$10.00.

WHILE no one can deny Dr. Clendening the right to disregard any critic who finds fault with the omission of what the latter may think should appear in the text, the criticism still holds but in no way detracts from the merits of his book. The author states



that his efforts are mainly the results of his own experience.

One clinician may prefer dilaudid as a sedative, another digifortis, digifolin or digalen as cardiac stimulants, still another may prefer anayodin for amebiasis, none of which is mentioned in the text, to those recommended by the author for their particular purposes. Such omissions by no means, however, lessen the value of the book. Its scope and extent, its literary qualities, the notes of historical value, the discussions

in which indications for various drugs are given, based upon physiological and clinical requirements should, as it has in the past, continue to make the volume a valuable addition to the physicians' library and office. It is a combination of materia medica and therapeutics by Dr. Clendening and others in a way that make the whole readily usable. There are many illustrations, charts, diagrams, and medical references and the printing is excellent.

Leon Bloch, Chicago.

## ABSTRACTS

SMITH, N. D., AND BROEERS, A. C.

*Melano-Epithelioma and Hemangio-Endothelioma of the Anus. S., G. and O., Vol. 60, No. 1, Jan., 1935, pp. 74-77.*

The authors report four cases of melano-epithelioma and hemangio-endothelioma of the anus. In one case of melano-epithelioma the tumor was found on the anterior anal wall. In spite of complete excision of the tumor and irradiation therapy, the patient died with wide-spread metastases 21 months later. The second case of melan-epithelioma was discovered during the routine microscopic examination of tissue removed during an operation for hemorrhoids. One hemangio-endothelioma was found in the anterior margin of the anus. It presented the appearance of a thrombotic hemorrhoid but caused no discomfort. Microscopic examination revealed its true nature. This patient was given 330 milligram hours of radium irradiation in the healing wound; three months later no evidence of a recurrence was found. The second hemangio-endothelioma was discovered during the routine microscopic examination of tissue removed during the excision of an anal fistula.

The prognosis in cases of melano-epithelioma is grave, but it is not beyond reason to expect that the tumor could be discovered early enough and completely excised. The prognosis in cases of hemangio-endothelioma is good; they grow less rapidly and metastasize less frequently.

Two of these cases prove the value of routine microscopic examination of tissues removed at operation.

Four figures accompany the article.

N. M. Percy, Chicago.

E. A. DANIELS.

*Early Diagnosis in Rectal Cancer and Prognosis on the Basis of Dukes' Classification. Can. Med. Journal, Dec., 1934, p. 612-616.*

Early rectal cancer gives few and indefinite signs, when there are definite signs and symptoms it is inoperable. The lesion always begins in the mucosa and extends through the rectal wall into the perirectal tissues. Dukes' classifies growths A, B or C, according to degree of direct spread, A being limited to the wall, involving but not beyond the muscularis, B extends into the perirectal tissue, but there is no glandular involvement; in C the regional lymphatics are involved. Pain and bleeding only occur with involvement of the extra-rectal tissues and the cutting off of the circulation to the growth causing ulceration.

The prognosis in rectal cancer is grave only in late cases, the C cases of Dukes' classification, the disease remaining localized for a long time. Vague symptoms of, change in bowel habit, backache, frequency of urination

call for rectal and proctological examination. With the proctoscope from the appearance of the growth, whether sloughing and friable or not, or whether fixed or not, one can get some idea of what stage has been reached.

Dukes examined histologically 215 specimens removed at operation; of these 18% were A cases, and 47% were C cases. Sixty cases were followed up after excision. Of these 15 were A, 24 were B and 21 were C cases. Three years later 86% of A cases were alive and well, 73% of the B cases, and 19% only of the C cases.

The classification would seem to be a very useful means of estimating prognosis.

R. H. M. Hardisty, Montreal.

H. O. OUGHTERSON AND M. T. SHELTON.

*End Results in the Treatment of Carcinoma of the Colon. Yale Jour. Biol. and Med., 1934, VI, p. 435.*

The authors conclude, from their own experience in the New Haven Hospital that cancer of the colon is being more effectively treated than either cancer of the stomach or rectum. A higher percentage of patients with cancer of the colon is being admitted to Hospitals in New Haven than those with cancer of the stomach, though not as high as those with cancer of the rectum. A higher percentage of patients with cancer of the colon are seen earlier, and the mortality at operation is lower. These factors are assisted by slower growth of the tumor and the tendency to late metastases. More than 42% should have an opportunity for a radical attempt at cure. A 2 stage radical operation is important. The radical operation for cancer of the colon results in a higher per cent of 5 year cures than does operation in any other portion of the intestinal tract.

Franklin W. White, Boston.

K. BLOND.

*The Pathology and Therapy of the Varicose Disease of the Rectum. Wiener Klin. Woch. No. 47, 1934.*

Nodules, fissures, periproctitis and pruritus of the anus are only different stages of congestive diseases of the rectum. The fistulas are veins of the hemorrhoidal plexus that become infected and filled with thrombi. If situated at the line of demarcation between the mucosa and the skin a fissure is the result. A dissection of the routes of the fistula should be done. In other cases, Pacqelinisation is necessary. An accompanying pruritus and almost always disappears after eliminating the underlying pathology. Such anal fissures or fistulas may often become starting lesions for propagation of secondary infections into the intra and extrahepatic bile ducts. The route for invasion is the hemorrhoidal plexus.

M. E. Gabor, Milwaukee.

## SECTION XII—"The Clinic"

### An Instance of Marked Abdominal Distension with the Probable Etiologic Factors Being Abnormal Endocrine Function\*

By

GEORGE B. DORFF, M.D.  
BROOKLYN, NEW YORK

**T**HE interrelation of the somatic and the skeletal systems and the endocrine systems must always be borne in mind when one is confronted with evidences of developmental arrest in the child. Symptoms seemingly of a non-endocrine nature which are accompanied by such somatic or skeletal maldevelopment should always be carefully evaluated for the possibilities that such symptoms may be manifestations of endocrine dysfunction.

One such case, where the complaint was abdominal distension, came under my observation. It is here presented as an example of the endocrine factor involved and the significance of that involvement from the differential and therapeutic standpoints. So that cognizance of these types may be taken and proper therapy administered as early as possible, this case is reported in detail.

#### CASE REPORT

*T. D.*, an Italian boy, aged 6½, was referred to the hospital† on September 5, 1934, with the complaints of pain, and enlargement of his abdomen. This enlargement had been noted by his mother for the past year; however, it had become more marked in the past two months. There was no concomitant nausea, vomiting or temperature. The abdominal pain was not acute and had its recent acute inception one week previous to admission.

The patient was of a full term normal delivery, and was the last of nine

children. He was of good size at birth; was breast fed only for a short period and then was placed on bottle feedings. Cod liver oil had not been given until the age of 1½ years; it had been taken until the age of 2. The only illness, measles, had occurred in early infancy. There was no history of constipation or diarrhea, although the patient often would have two to three bowel movements daily. His diet was varied, including fresh fruits and vegetables. He had grown, however, very slowly. The father had died of hypertension, at the age of 44 years; and four siblings died of pneumonia. The mother was apparently well.

An examination of the patient by the writer on September 5, 1934, exhibited a dwarfed, undernourished, fairly alert boy who presented marked abdominal distension. There was pallor, but no apparent jaundice. The head was not enlarged; his hair and skin were not dry. The eyes reacted to light and accommodation; the deciduous teeth were in bad condition; there were many carious teeth showing hypoplastic enamel; the sixth year molars were present but also lacked enamel. The tonsils were enlarged. There were some enlarged cervical glands. The bony chest was negative. The heart sounds were rapid but normal in character. The lungs were clear.

There was a marked distension of the abdomen which tended to bulge laterally. The umbilicus was flattened and the abdomen was generally tympanitic. There were no palpable masses nor was there any shifting dullness. Peristaltic waves could be made out and induced. Some very slight abdominal tenderness was present. Rectal examinations proved somewhat painful but no masses were felt (Fig. 1).

The extremities were not distorted in any way, and were proportional to the

rest of the body. His height on admission was 38 inches (normal 44.5-47.7 inches). His weight was 34 pounds 12 ounces (normal 41.0-50.8 pounds). Two small testes were present in the scrotum; the penis was small.

An admission diagnosis of "megacolon" was made with the possibility of its being congenital (Hirschsprung's megacolon).

Laboratory studies were as follows:

|                        |         |
|------------------------|---------|
| (October 2, 1934):     |         |
| Haemoglobin (Sahli)    | 46%     |
| RBC                    | 3.6     |
| WBC                    | 9,400   |
| Platelets              | 300,000 |
| Staf Granulocytes      | 3       |
| Segmented granulocytes | 60      |
| Lymphocytes            | 24      |
| Monocytes              | 11      |
| Eosinophiles           | 1       |
| Basophiles             | 1       |

There were marked poikilocytosis and anisocytosis but no nucleated red blood cells. Dr. Charles Feingold of the Haematology Department was of the impression that there was a marked hypochromic anemia, probably nutritional.

A fasting blood analysis revealed the following:

|                  |         |
|------------------|---------|
| Glucose          | 86 mgs. |
| Urea N.          | 8.5     |
| Creatinine       | 1.0     |
| Chlorides        | 587     |
| Cholesterol      | 140     |
| CO <sub>2</sub>  | 47      |
| Serum Calcium    | 11.5    |
| Serum Phosphorus | 3.8     |

The Wassermann test was negative. The Mantoux 0.1 mg. and increased to 1.0 mg. was negative for tuberculosis. A casual urine examination showed no abnormal findings. A phthalein functional test showed 60% elimination for the first hour and 15% in the second hour—a total of 75%. A Mosenhath test on two occasions returned the following: (November 5, 1934):

\*From the Endocrine Clinics of the Department of Pediatrics of New York University, College of Medicine, and the Children's Medical Service of the Third Medical Division, Bellevue Hospital, and Beth-El Hospital.  
Presented before the New York Endocrinological Society February 27, 1935.  
Submitted April 16, 1935.

†I am indebted to Dr. Harry R. Litchfield of the Pediatric Service of Beth-El Hospital for the opportunity of studying this case.

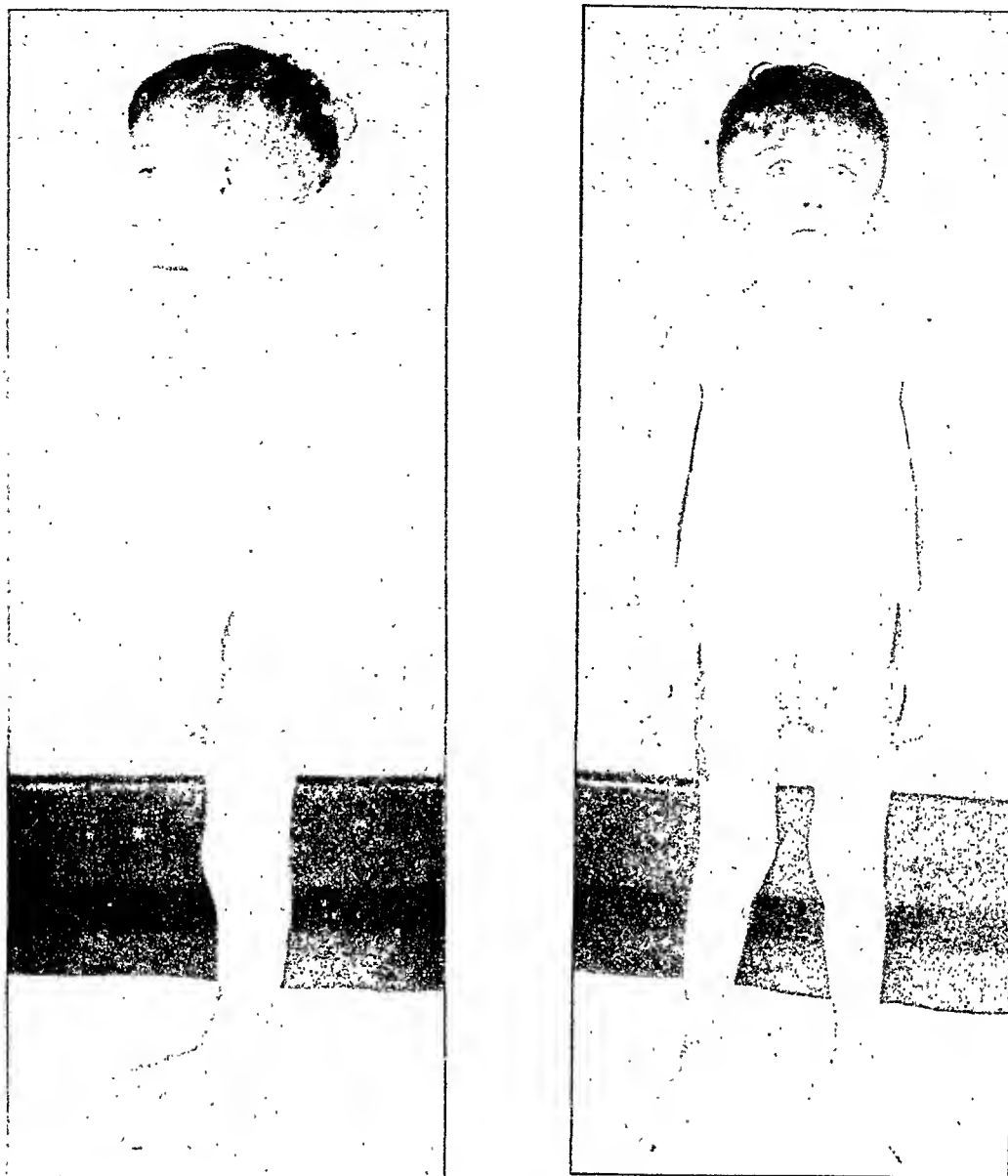


Fig. 1. Age 6½ years. Note abdominal distension.

|                   | S A. M. | 10 A. M. | 12 N. | 2 P. M. | 4 P. M. | 7 P. M. | 10 P. M. |
|-------------------|---------|----------|-------|---------|---------|---------|----------|
| Sp. Gravity       | 40 cc.  | 18       | 75    | 75      | 60      | 40      | 50       |
| Sp. Gravity       | 1033    | 1032     | 1028  | 1028    | 1027    | 1035    | 1038     |
| November 9, 1934: |         |          |       |         |         |         |          |
| Amount            | 30 cc.  | 15       | 25    | 10      | 25      | 28      | 25       |
| Amount            | 1033    | 1035     | 1034  | ...     | 1030    | 1034    | 1023     |

Examination of the stool on several occasions showed it to be bulky, greyish in color and foul smelling. Amylase, and a normal amount of fat were present; ova, and *B. dysenteriae* were absent.

A water test for any parenchymal liver damage (Adlersburg) showed an intake of 1000 cc. of water and an output of 985 cc. of urine (normal). Several basal metabolic readings were in the neighborhood of plus 100. Obviously, the rate, as estimated, was erroneous.

An X-ray examination at the time of admission, September 6, 1934, by Dr.

Max Dannenberg, as revealed by the flat film taken in the erect position, disclosed a considerable amount of gaseous distension with evidence of fluid levels in the intestinal loops.

Further examination after a barium, colon enema showed no definite evidence of obstruction or true intrinsic defects. There were a generalized atony and dilatation of the colon and at the flexures (Fig. 2).

The bones of the skull were normal. The sphenoids were clouded. The sella turcica was normal.

A roentgen study, September 22, 1934, (by the writer), of the osseous

development, showed the presence of four small carpal centers in each hand. The distal epiphysis of the left ulna was pin point, and that in the right was absent. The epiphyseal nucleus for the head of the radius was absent (the average normal appearance is at 5 years—patient was 6½ years). There was no evidence of any rachitic changes. There was a moderate generalized halisteresis present in the diaphyses of the long bones, particularly in that of the knee and elbows, and some in the hands. Transverse lines of arrested growth were present about ¼" below the distal part of the femur and at the distal part of the tibia. In all, bone development was retarded about two years.

*Diagnosis:* Because of the absence of abdominal distension or gastro-intestinal symptoms in early infancy, and the locally insufficient dilatation of the intestinal loops as is characteristic of



Fig. 2. (Hand) Aged 6½ years. Eleven weeks after thyroid medication. Note retarded centers of ossification in the carpus, and the presence of the pin point epiphysis of the ulna which was absent on admission.

Hirschsprung's congenital megacolon, this latter diagnosis was discarded and the diagnosis of hypothyroidism was substituted. This diagnosis of hypothyroidism was based on the findings of dwarfism, atonic intestinal tract, anemia, and marked delay in osseous development.



Fig. 3. Left (7208). Note dilatation and absence of haustral markings.

**Treatment:** The patient was placed on a full hospital diet and was given desiccated thyroid, 1½ grains daily, (September 14, 1934.) This remedy was exhibited for about eleven weeks.

It was noticed that, while the patient was in the hospital, he had a voracious appetite at all times and constantly had to be given extra portions of food. When these larger meals were given, the abdominal distension became more prominent; however, there occurred no such intestinal upsets as diarrhea, nausea or vomiting.

On November 30, 1934, after 11 weeks of thyroid therapy, the patient was placed on a standard, three day, Schmidt's test diet. During this time, the standard diet with some slight modification was given, and the stool therefrom was collected for examination.\*

Following is the analysis of the stool which was examined after it had been collected over the test period for the Schmidt diet:

"The stool appears soft, bulky, grayish and unformed; on microscopical examination there is present much cellular debris and an occasional starch granule; no undigested muscle-fibers are visible. There are moderate amounts of neutral fat, larger amounts of fatty acid and soap. After the addition of 30% acetic acid and heat, the specimen shows large amounts of neutral fat globules."

"The analysis of stool shows good digestion and absorption of all three types of foods. In addition, the fats show good splitting. In the presence of such good absorption, and the absence of stinted muscle in the stool, I feel, in spite of the gross fat present, that pancreatic juice in sufficient quantity to provide normal absorption probably is reaching the intestine. Even if the large amount of fat found on microscopical examination was borne out by the analysis, it would be distinctly unusual to have only the fat-splitting ferment deficient in pancreatic juice."

A roentgen examination on November 20, 1934, (about two weeks prior to patient's discharge), showed, by barium colon enema, that the intestinal tract now presented definite tone and definite haustral markings. The barium at this time was evacuated in 1½ hours, whereas at the first examination there was retention of about 12 hours for the same amount of barium used in the enema.

A roentgenogram of the wrists and hands at this time showed that, while



Right (7737). Note presence of increased intestinal tone and haustral markings after thyroid therapy.

the four carpals present originally were enlarged very slightly, if at all, the distal ulnar epiphyses now were present, though small, in both wrists. Also, the epiphysis of the left ulna noted on the first examination had somewhat increased in size. The period of treatment with thyroid medication, however, had been too brief for one to expect any marked bone advance, but nevertheless, the progress was sufficient to indicate the many varied benefits of the thyroid therapy (Fig. 3).

On December 10, 1934, the patient was discharged. A check up at this time showed that, after eleven weeks of dietetic and thyroid therapy, his ab-



(Elbow). Note absence of epiphysis for the head of the Radius, and for the internal condyle of the humerus. Bone retarded about 2 years.

\*I am indebted to Dr. Milton B. Handelsman, and to Dr. Lewis A. Golden of J. P. Pratt's Research Department of Tufts Medical School for the analysis and report of this stool.

*Synopsis of Stool Analysis:*

| Diet:                    | Fat   | Carbohydrates | Nitrogen |
|--------------------------|-------|---------------|----------|
| Schmidt's Diet           | 333 G | 573 G         | 48.90 G  |
| Omitted from diet        | 129   | 217           | 10.75    |
| Actually given in 3 days | 204 G | 356 G         | 38.15 G  |

*Analysis of Stool:*

|                      | Fat                    | Carbohydrates         | Nitrogen          |
|----------------------|------------------------|-----------------------|-------------------|
| Dry Weight           | 67.0 G                 |                       |                   |
| Fat in dry Stool     | 38.5%                  |                       |                   |
| Amount in Stool      | 25.80 G                | 3.0 G                 | 4.35 G            |
| Therefore % Absorbed | 87.35%<br>(normal 95%) | 99 plus %<br>(normal) | 88.5%<br>(normal) |

*Analysis of the fat unabsorbed:*

|             |         |         |
|-------------|---------|---------|
| Fatty acid  | 11.48 G | (44.5%) |
| Soap        | 3.90 G  | (15.1%) |
| Neutral fat | 10.42 G | (40.3%) |

demen definitely had decreased in size, though it was still quite distended. Yet, the lad was comparatively comfortable, as was attested, and he was much more alert. During this three months' period, he had increased 2 inches in height, and he had gained 5 pounds in weight (in spite of having an upper respiratory infection for one week during the latter part of his hospital stay).

## DISCUSSION AND COMMENT

Hypothyroidism in a mild or masked form differs so greatly and in so many respects from myxedematous cretinism or marked hypothyroidism that it is sufficiently important to warrant careful study and constant alertness for the many and varied manifestations of such symptoms of mild hypothyroidism (1).

In the case here cited, the outstanding and varied symptoms were dwarfism, an apparent malnutrition, anemia and abdominal distension. Such a picture presented a possible case of masked hypothyroidism. Then, subsequent X-ray findings of an atonic intestinal tract, and particularly of osseous delay in the time of appearance of the carpal centers and epiphyseal nuclei affirmed the suspicion of hypothyroidism.

However, various other possible diagnoses presented themselves, as celiac disease, juvenile congenital lues, rickets and Cooley's erythroblastic anemia, all of which might be associated with retarded osseous development. These affections therefore were all individually considered, for the case in hand and eliminated for the following reasons:

**Celiac Disease:** The absence of any acute history, the tolerance to carbohydrates as well as to other foods when on a full diet, the comparatively good absorption of the

three types of food when on a Schmidt test diet, and a normal serum-calcium quantity all ruled out celiac disease.

**"Renal Rickets":** Physical, chemical and roentgen studies excluded the possibility of renal rickets.

**"Cooley's Erythroblastic anemia":** A blood examination, and a roentgen study of the skull and long bones eliminated this possibility.

**Juvenile congenital lues:** The absence of typical physical signs and roentgen findings, of the long bones, and a negative Wassermann reaction excluded this possibility.

**Infantilism** due to organic pancreatic involvement: The comparatively normal stool and the good digestion and absorption of the three types of food, showed good function of the pancreas and therefore eliminated this affection. Furthermore, the writer is not aware of any osseous involvement with organic pancreatic lesions, and in this patient there was osseous retardation.

**"Fermentative" Diarrhea:** (2). Because of the two or three bowel movements per day and because the results obtained by stool examinations after the Schmidt diet approximated Schmidt's figures for fermentative diarrhea, this condition too subsequently had to be considered.

However, fermentative diarrhea was ruled out because the two or three bowel movements were not diarrheal in nature, and because there was no increased intestinal motility—the carmine in the test diet appeared in forty-four hours.

Therefore, in view of the above considerations and in the presence of the dwarfism, the anemia, the abdominal distension, the atonic intestinal tract and the retarded osseous

This journal will pay 50 cents  
each for  
COPIES of the APRIL, 1935  
Issue.

Please write before sending  
the copies to The American  
Journal of DIGESTIVE DIS-  
EASES AND NUTRITION

435-455 Lincoln Bank Tower  
FORT WAYNE, IND.

**TILDEN has Kept Faith  
with Physicians**

## ELIXIR MALTOPEPSINE (Tilden)

Consists of DIOSCOREIN, LACTIC ACID, DIASTASE, PEPSIN with acidic and other ingredients, combined in a manner exclusive with Tilden.

MALTOPEPSINE (Tilden) for many generations has been prescribed as a dietary aid in conditions involving gastric and intestinal upsets. It is a very palatable vehicle for prescriptions carrying such drugs as IODIDES, BROMIDES, SALICYLATES, and NUX VOMICA, and guards against any untoward effect of these substances on the metabolism.

MALTOPEPSINE (Tilden), like all prescription specialties produced by The Tilden Company, is labeled according to law, advertised only to the medical profession, manufactured under strict scientific control, and offered only after years of thorough clinical success.



Literature will be furnished confidentially  
to physicians only on request.

## The Tilden Co.

The Oldest Pharmaceutical House  
in America

New Lebanon, N. Y.

St. Louis Mo.

D 7-35

development, a diagnosis of masked hypothyroidism was considered most probable; the correctness of this diagnosis apparently was substantiated by the favorable response of the patient to thyroid therapy. Within a period of about eleven weeks of such therapy, he showed marked improvement; a gain of height of two inches, an increase in weight of five pounds, a progressing osseous development, a definite increase in intestinal tone and general feeling of well being.

However, the excretion of excess fat in the patient's stool was per-

| Normal Averages<br>(Schmidt's) | Dry Wt. | % Fat in<br>Dry Stool | Fat Metabolism                     |                                |                |
|--------------------------------|---------|-----------------------|------------------------------------|--------------------------------|----------------|
|                                |         |                       | Am't. Fat<br>excreted<br>in 3 days | % Fat<br>in Food<br>unabsorbed | % Fat<br>Split |
| Reported case*                 | 54.3 G  | 23.24%                | 13.78 G                            | 5.50%                          | 60.5%          |
| Fermentative Diarrhea          | 67.0    | 38.50                 | 25.80                              | 12.65                          | 59.6           |
| (Schmidt's)                    | 127.4   | 20.90                 | 25.56                              | 11.47                          | 80.0           |

plexing and at present remains unexplained, unless one might consider the excess as a functional, rather than as an organic defect of the pancreas, or as a consequence of a supercaloric diet, which the patient's voracious appetite made quite likely.

What relation, if any, there is between the excess excretion of fat in this patient's stool with the presence of his halisteresis is not certain. However, that an excess of fat may tend to inhibit the absorption of calcium by forming insoluble calcium soaps and thus indirectly causing the halisteresis, is a possibility to be considered. Or, if an excess elimination of calcium in the stool is causing "fixation" of the fat, such also must be considered. As to proof of this phenomenon, a study of the calcium balance may have helped, but unfortunately such could not be made. However, had such a study been made, the findings of a negative calcium balance might have accounted for the halisteresis, but would not have accounted for the delayed appearance of the ossification centers.

### SUMMARY

1. An Italian boy, aged six and one-half, dwarfed, and showing a marked abdominal distension was admitted as a case of congenital

\*Allowances, however, must be made for the food omitted from the Schmidt diet because of the patient's dislike for the same and for which other food had to be substituted. Under these conditions higher values would have been obtained had not the diet been modified.

megacolon (Hirschsprung's disease). The patient presented evidences of anemia, malnutrition, an atonic intestinal tract, and marked osseous retardation (equivalent to about two years), as revealed by X-ray appearance of his carpal centers and epiphyseal nuclei. In view of the above findings several diagnoses were considered and eliminated: namely, celiac disease, renal rickets, juvenile congenital lues, Cooley's erythroblastic anemia and pancreatic infantilism.

2. The diagnosis of congenital megacolon was discarded because of the late onset of the intestinal disturbance, the absence of obstinate constipation and incomplete Roentgen findings, and the diagnosis of hypothyroidism was substantiated. This diagnosis was based upon findings of dwarfism, an atonic intestinal tract, anemia, and retarded osseous development. The patient therefore was placed on thyroid medication and a full diet.

3. After a period of eleven weeks of such therapy the patient showed the following:

- A general feeling of well being.
- An increase of two inches in height and an increase of five pounds in weight.
- An increased tone in the intestinal tract.
- An advance in the osseous development—slight yet sufficient for this period.



## Constipation's Baffling Complications

with the attendant biliary stagnation are materially relieved with bile salts in combination with phenolphthalein and cascara sagrada as combined in

## TAUROCOL Bile Salts Tablets

TAUROCOL is a combination of bile salts, extracts of cascara sagrada, phenolphthalein and aromatics and is an agent recognized by the medical profession and widely prescribed for about a quarter of a century.

Samples of Taurocol on request. We will gladly furnish clinical test record forms if you wish them . . . just tell us how many to send.

### The Paul Plessner Co.

Detroit - - - Michigan  
J. D. 7-35

4. Before the patient was discharged, he was given a modified three day Schmidt test diet and his stool then was studied. Good digestion and absorption of all three types of food were found. However, there was present an excess of fat.

5. This presence of excess fat in the stool was perplexing and was finally considered compatible with a functional disorder of the pancreas.

6. The possible significance and the correlation, if any, of this excess fat in the stool with the retarded bone development and particularly the halisteresis in this case, are discussed briefly but not accepted as definite or final.

7. The importance of recognizing seemingly remote symptoms and of considering them as possible clues towards the diagnosis of masked hypothyroidism are emphasized and discussed.

### REFERENCE

- Dorff, George B.: Masked Hypothyroidism in Children: Osseous Development as an Aid in Diagnosis. *J. of Pediatrics*, 6:75, 1935.
- Pratt, Joseph H.: The Diagnosis of Chronic Pancreatic Disease, *International Clinic of N. Am.* 2:154, 1931, J. B. Lippincott Co. Pub., Philadelphia.

## SUBSCRIPTION BLANK

American Journal of Digestive Diseases and Nutrition  
435-455 Lincoln Bank Tower,  
Fort Wayne, Indiana.

Enclosed please find \$6.00 (Foreign \$7.00) for one year's subscription to the American Journal of Digestive Diseases and Nutrition.

Name .....

Street .....

City ..... State .....



# SECTION I—*Clinical Medicine: Diseases of Digestion*

## On the Etiology of Peptic Ulcer\*

### An Analysis of 70 Ulcer Patients

By

SAMUEL C. ROBINSON, M.D.  
CHICAGO, ILLINOIS

THIS paper deals with the physical builds of seventy "peptic" ulcer patients and their personalities. Some phases of pathology are discussed as well as interesting features of incipient ulcer. Conclusions from this factual information are shown to support the neurogenic theory of "peptic" ulcer. Briefly it claims that fear, anxiety and apprehension stimulate the vegetative system to the stomach and duodenum resulting in hypermotility, hyperchlorhydria and vascular spasm. This spasm in turn leads to thrombosis, ischemia, necrosis and ulceration. Other factors such as hyperacidity, focal infection, diet, etc., are shown to have absolutely nothing to do with the etiology of this disease.

#### RACIAL SELECTIVITY

"Peptic" ulcer has never been found in the lower animals and its production artificially is still debatable. If a portion of the mucosa of the dog's stomach is removed, the defect heals very rapidly without much scarring, new mucous membrane filling in the lesion. This rapid healing process takes place in the presence of natural acidity, or added acidity (1) or any form of diet. The production of chronic peptic ulcer in the lower animals has baffled the experimental physiologist for years and in the opinion of Mann "Chronic peptic ulcers have never been consistently produced experimentally in the gastric mucosa by any method" (11). By means of circuitous anastomoses, some chronic ulcers have been produced but their value is open to question. They are atypical and distort normal anatomy and physiological function to so great an extent as to make any conclusions of doubtful value when applied to the human. Incidentally, incisions in the mucous membranes of human stomachs heal rapidly (2).

"Peptic" ulcer occurs very rarely in the Negro race (3). The New Orleans Board of Health (4), citing mortality statistics for a decade—1919-20 shows an ulcer death rate of .123% among white population and .043% amongst negroes. Even this low percentage would be reduced further if the interbreeding factor could be computed and deducted. The Bellevue Hospital, New York from 1904-1922, gave a total of 120 cases of gastric ulcer of which only two were negroes. Dr. Bergsma (5) reports frequent ulcers in the colored race in Abyssinia. These ulcers are produced on a

chemical basis, the native diet consisting of sour bread and 50% capsicum or cayenne pepper, a mixture which was strong enough to cause blisters on Dr. Bergsma's lips. The ulcers are multiple, occur all over the stomach with formation of fibrotic rings. There is no resemblance to the typical single ulcer in its common location along the lesser curvature of the stomach and the first inch of the duodenum. The present paper is attempting to elucidate only this particular type of ulcer with the classic history of distress after meals, relieved by food, hyperacidity, chronicity with exacerbations and remissions.

"Peptic" ulcer is not found in the lesser pigmented races of the world, either before or after their contact with civilization. The Mexican Indians are free from ulcer although they live under horrible hygienic conditions and their diet is coarse and deficient (6). Dr. McCarrison (7) in nine years of practice, performed 3600 operations on primitive tribes in the Himalaya Mountains and found no ulcers, mucous colitis or appendicitis. The white race living under primitive conditions is less prone to ulcer. Centuries ago, before the advent of the machine age, the disease was very uncommon. Older text books devote very little space to it. But with the turn of the century the disease has been on the increase (8). A highly competitive and more complex civilization has made existence more precarious for most of us; as a result tensions have increased. Those who are on the firing line of this life-struggle, such as salesmen, specialists in all fields particularly medicine, executives, etc., are more prone to this disease.

We have seen that the lower animals do not develop ulcers, the Negro and lesser pigmented races seldom if ever do and the Caucasian race rarely does under primitive conditions.

This is a unique selectivity in the annals of disease. It is obvious that we need the complexities of civilization impinging upon certain types of the white race to produce "peptic" ulcer. It was an attempt at a more careful study of the physical characteristics and personalities of the white man who develops "peptic" ulcer that prompted the analysis of seventy ulcer cases, the data of which are herewith presented.

#### THE ULCER BUILD

Long before anthropometric measurements were extensively used by science, physicians noted that the

\*From the Department of Medicine, Woodlawn Hospital, Chicago.  
Submitted May 29, 1935.

ulcer individual is a long and lanky person. They have likewise associated a vague picture of his personality *viz*—a young man with considerable dynamic energy, with quick reaction-time and of a high tension type. The laboratory has applied its more accurate technique to this "hunch" of the older practitioner, with strengthening verification.

The most exhaustive study of physical types made in this country is that of Dr. George Draper (12) at the Constitution Clinic of the Presbyterian Hospital in New York City. His book "Disease and the Man" might serve as a stepping stone in the elucidation of most of the common disease entities.

Here we find a scientific appraisal and classification of physical types, the basic ingredient of disease itself. Complete anthropometric measurement, as carried out by Dr. Draper, is a very elaborate procedure and re-

series of seventy cases, only three weighed 170 pounds and one 180 pounds. None weighed more.

The ulcer patient's *chest measurement* of this series follows the normal more closely in the smaller brackets than he does in the weight curve (Figure 2). While there are more underweights among the ulcer cases, the number of low chest measurements is about equal to the average run of cases. But there is a sharp dropping off in the larger chest groups so we find no ulcer patient with a chest measurement over thirty-nine inches in this series. In a similar control group of average normal measurements there are seven. This is the measurement that more sharply differentiates the linear from the lateral types and we find the ulcer patient breaking away abruptly from the larger groupings.

The *ponderal index*, or the relationship of height to

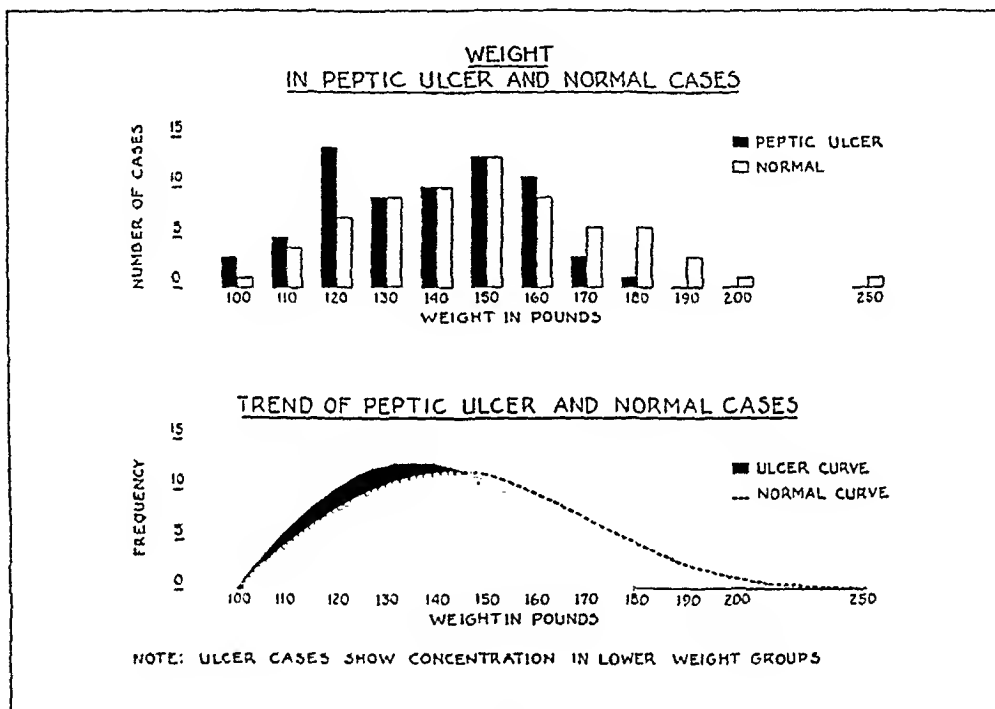


Fig. 1

quires much time and special instruments. But the simpler measurements available to the average practitioner can throw much light and classify the ulcer "race," if not so meticulously as Dr. Draper, at least helpful in singling out the striking limitations of measurements into which this group falls.

#### MATERIAL STUDIED

**Weight:** An analysis of the seventy cases of "peptic" ulcer of this series (proved by X-ray, history and physical findings) shows that the type is narrow and linear. There are very few overweights in this group as shown in Figure 1. They are more often underweight altho a definitely large percentage are about normal in weight. It will be seen that they outnumber the average person in the groups up to 150 pounds and fall off rather sharply in the heavier groups. Very few ulcer patients weigh over 180 pounds. The diagnosis of "peptic" ulcer on any person weighing over 190 pounds should be seriously questioned. In this

weight, aims at a more accurate portrayal of human build. This index is arrived at by dividing the weight in pounds by the height in inches. Many advise reducing these measurements to millimeters and grams but the ultimate result seems to be the same. Figure 3 shows the graphic presentation of these calculations and demonstrates more vividly than any of the other diagrams the narrow morphological range of the "peptic" ulcer type.

The *chest circumference-height relationship* is another method of classifying the linear and stocky build and is obtained by dividing the chest circumference by the height. (Figure 4) It correlates the lateral and linear measurements and offsets possible errors inherent in their separate comparisons. We may have two individuals each with a chest circumference of 37 inches yet one may belong to the lateral type being only sixty-two inches tall, the other to the linear type being seventy-three inches tall. Likewise the ponderal index by correlating the height to the weight

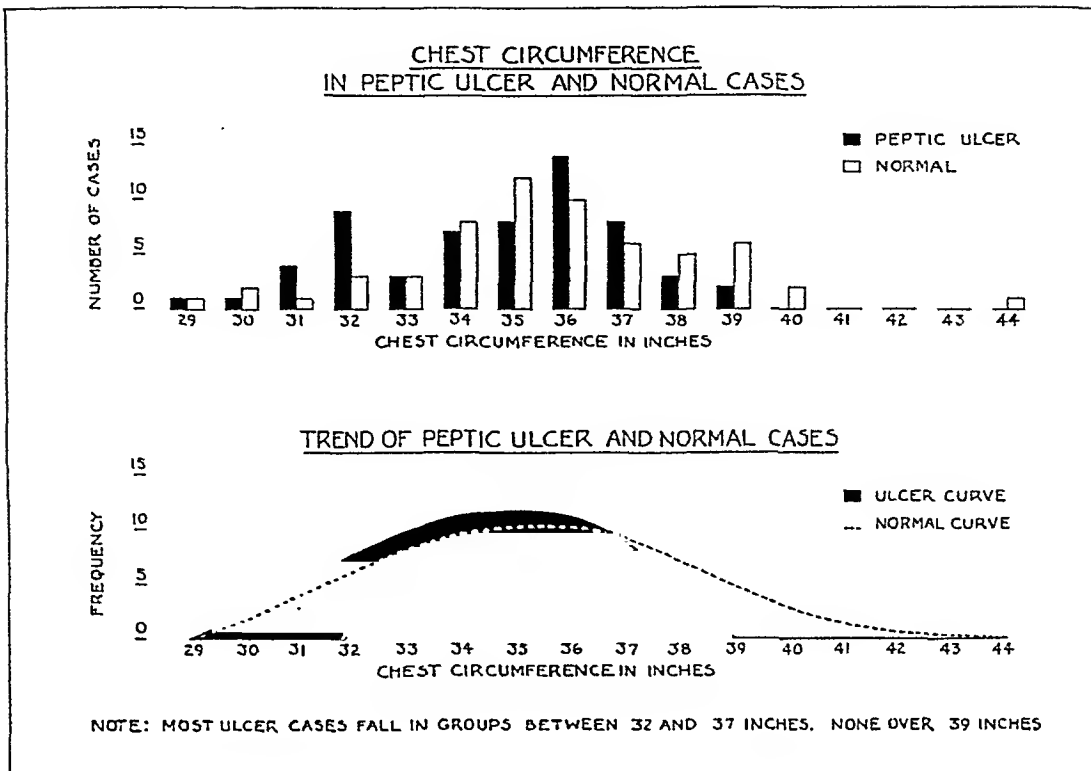


Fig. 2

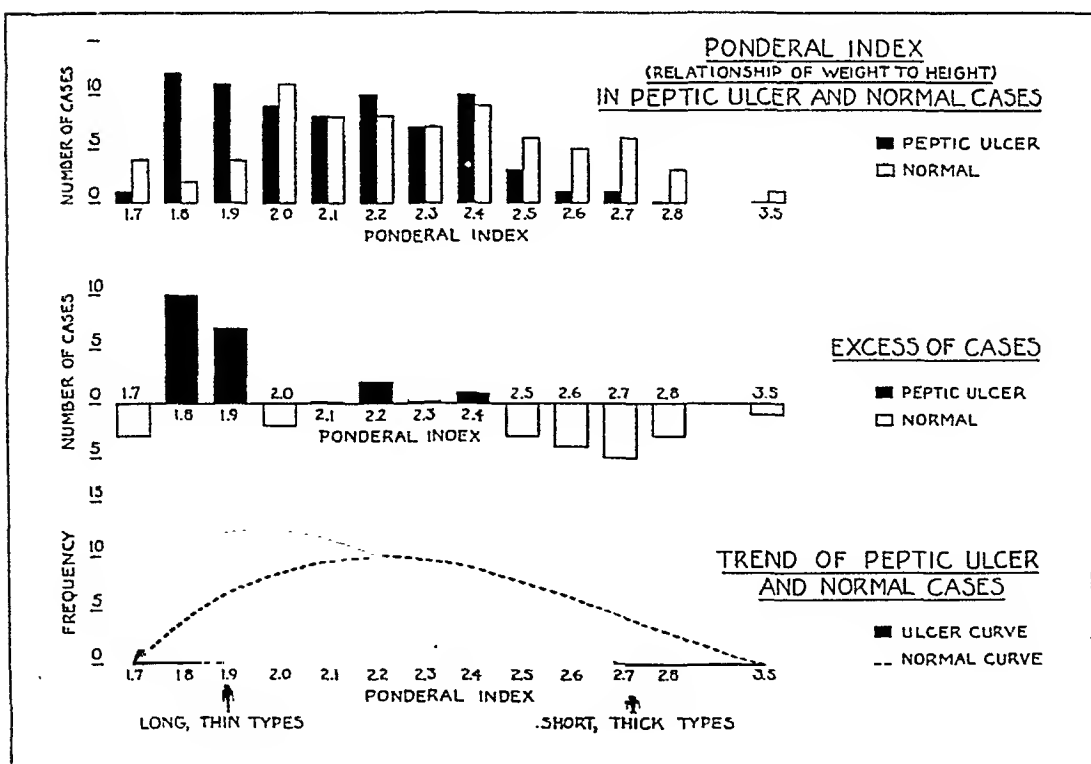


Fig. 3

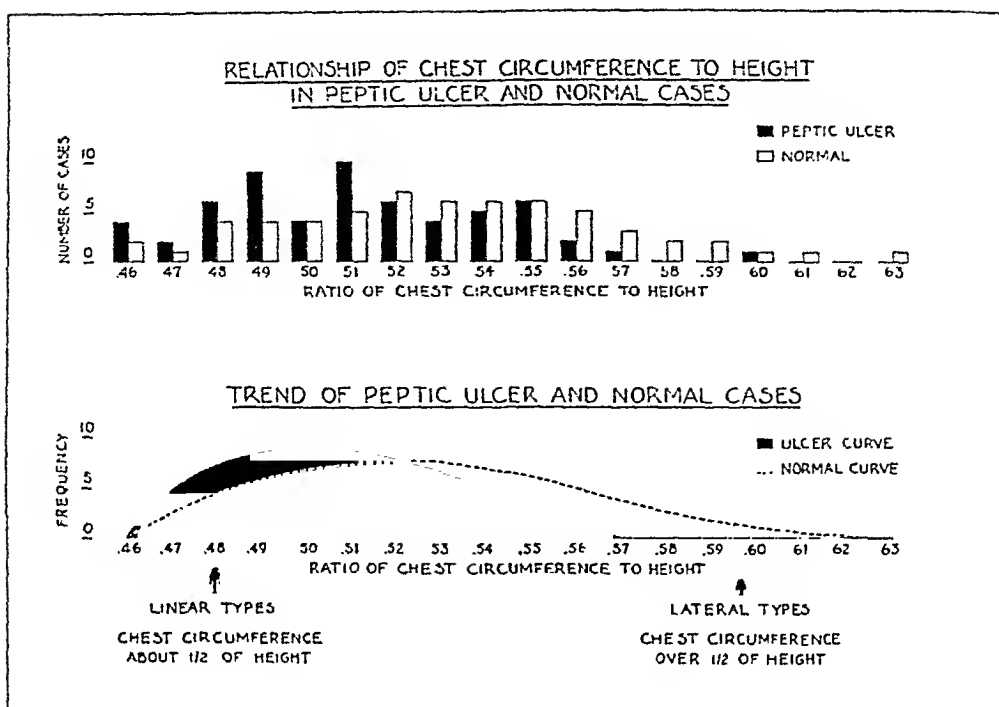


Fig. 4

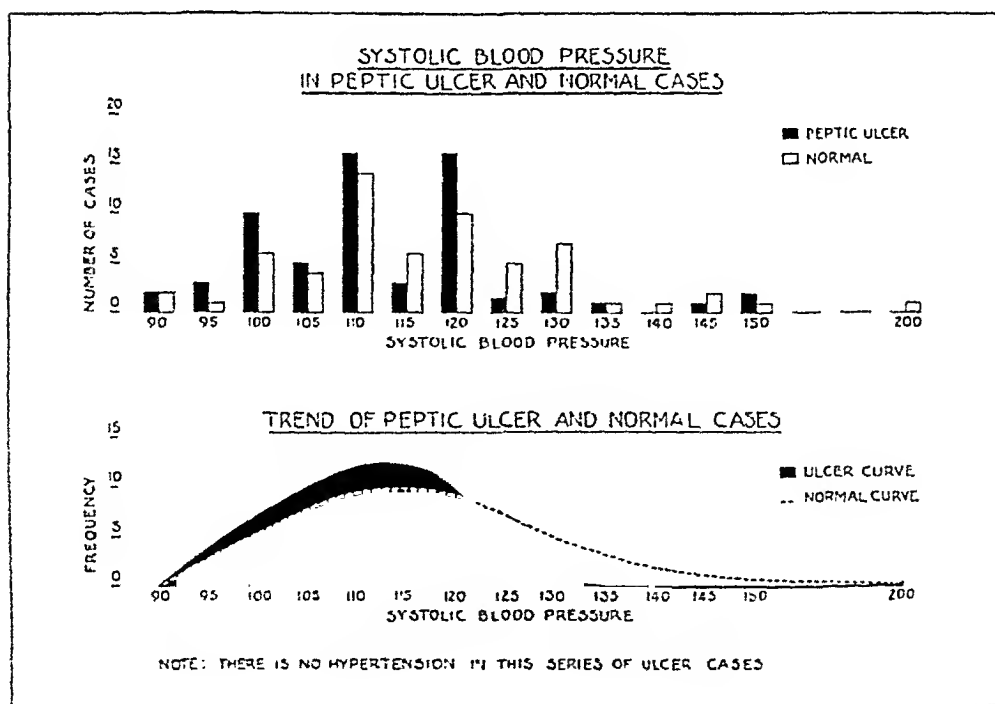


Fig. 5

assigns one individual weighing 160 pounds to the short and stocky group and the other of equal weight but eleven inches taller to the long and thin group. These comparative tables show that all the "peptic" ulcer patients belonged to the long and thin morphological type. No lateral build individual was among the 70 ulcer patients studied in this group. These findings are in complete agreement with those of Dr. Draper. In addition a few of his other measurements might be added. The face is broader in its upper half tending to taper sharply to a pointed chin. The upper jaw is frequently somewhat narrow and the upper median incisors project over the two lateral incisors. The angle of the mandible tends towards the acute. The palpebral fissure is consistently wide.

These fixed physical measurements of the ulcer patient direct our attention to the rôle of heredity in the etiology of this disease. The germ plasm alone transmits the potentialities for physical differentiation in the animal and human and plays the deciding part in our neuro-psychological make-up. Evidence of several ulcer patients in one family abounds in the literature and was found in this series.

*Miscellaneous Findings of Seventy Cases.* In this series, there was practically no hypertension. One patient with a blood pressure of 150 was omitted because an ascending urinary infection including pyelonephritis was his immediate complaint, the ulcer having been quiescent for ten years. Dr. Hartman (13) studied hypertension in ulcer patients with and without hemorrhage. He too reports hypotension to be the common finding in ulcer patients but does report six and nine percent of hypertension in his series altho actual blood pressure figures are not cited. Dr. Frank Smithies (14) found 14.7% with hypertension and arteriosclerosis.

In this series the relationship of males to females was 6 to 1. Some of the females showed masculine traits. This is also pointed out by Dr. Draper. One wore a shirt, collar and tailored suit and was in charge of large stenographic department. She was virile, dynamic and aggressive.

*Personality.* This rather definite build houses a personality of almost equal definiteness. It is relatively easy to present the anthropometric measurements of the ulcer patient but a portrayal of his personality is much more difficult. It is true that we have no comparable instruments for measuring personality but a sensitive and observing clinician has available a wealth of material in the statements of his patient especially if properly elicited. His behavior, his facial features and his finer fleeting changes help the intuitive sense in interpreting his story and give deeper meaning to some of the chance or casual remarks. Certain expressed attitudes occur with such frequency as to become characteristic of the group. In the seventy ulcer cases observed, as well as among those described in the literature, there is a striking agreement about the personality of an ulcer patient.

He is keen, intelligent and active rather than lethargic. Dr. Crile refers to him as the hyperkinetic type. His activity is fluctuating rather than sustained chiefly because his endurance is limited and he requires frequent rest-periods. His energy is often divided amongst several enterprises rather than concentrated

in a single channel and yet he is not satisfied with ordinary achievement. He is inclined to be over-precise and holds himself up to a high standard of performance. "My conscience would not permit me to do inferior work, I must give my best to it." Externally he may show a certain aggressiveness but this behavior often covers a real timidity. He is full of bravery in theory but extremely cautious in action. He proceeds with care and travels slowly feeling his way all the time and recoils swiftly when on the wrong trail. This caution is carried into his habits, dietary and otherwise. "I cannot understand why I should have an ulcer. I have been so terribly careful about my food all my life. Never ate spices or very hot foods. I order eggs most of the time when I eat out. Take no chances on cooks' mixtures." He is fearful, apprehensive and easily excited with the result that events which would leave a more stable person untouched, upset and worry him. He takes the world too seriously, himself, relatives and friends. He worries about all of them. Because of his conscientiousness, he soon takes on more responsibility than he is able to carry. He grows more and more weary and an exacerbation of the ulcer syndrome takes place.

Some ulcer patients display a very calm exterior and, at first glance, would seem not to belong to the worrying or tense type. They deny it. But as they unfold their stories they reveal their fears and sensitive make up. In a very few, it is difficult to elicit very much nervous unrest. But it is known that vegetative stimulation may take place on a subconscious level.

#### ULCER BEARING AREA

The site of the lesion is one of the most striking of all the interesting features of "peptic" ulcer. It singles out about four to five inches of the entire length of the twenty odd feet of the gastro-intestinal tract. (15) In the stomach over 95% of the ulcers are bunched together within two inches of the *incisura*. (Figure 9) a few of the remaining

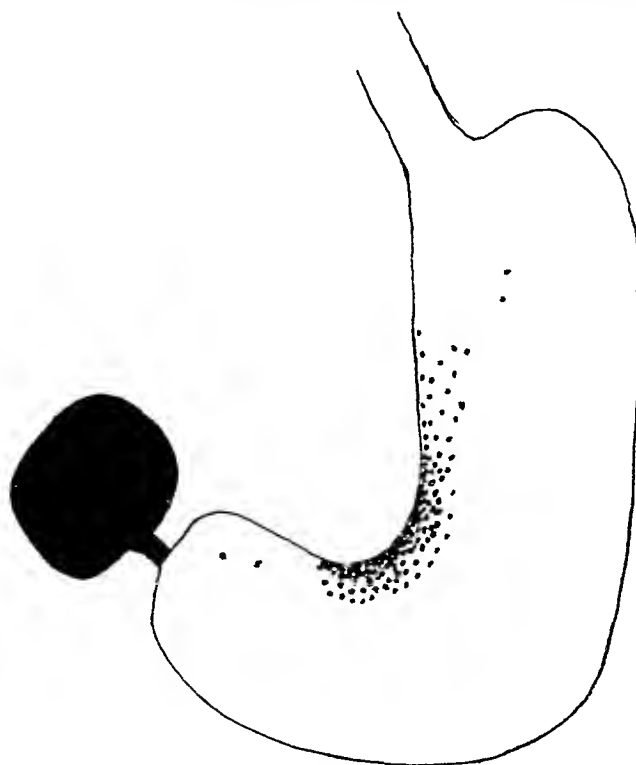


Fig. 9. Site of Gastro-Duodenal Ulcers (after Holmes and Hampton).

Fig. 9

are spread along the lesser curvature for a few inches towards the cardia and some towards the pylorus. In the duodenum practically all ulcers occur on the first inch of the anterior or posterior portion. (19) This predilection of "peptic" ulcers for so limited a region is quite unique for gastro-intestinal ulceration. The lesions in ulcerative colitis extend over the entire length of the colon and circularly in every quadrant of it. In typhoid fever and tuberculosis the ulcers occur throughout the entire length of the jejunum and ileum. The "peptic" ulcer shows a unique selectivity for the lesser curvature of the stomach and the first portion of the duodenum. The remaining 80% or so of the gastric surface is immune to the type of ulcer discussed in this paper. The ulcers that do occur here have a different etiology. They are atypical and have entirely different history, physical findings and response to therapy. (16) This emphasises the urgent need for ulcer classification.\* The *bizarre* picture of the atypical ulcer with its multitudinous and diversified symptomatology clouds the very constant mosaic of a classic "peptic" ulcer.

This lesser curvature of the stomach which is the site of over 98% of all gastric ulcers receives most of the innervation to this viscus. The vagus, coming down from the upper portion of the lesser curvature, sweeps down on this ulcer-bearing area and terminates the bulk of its fibrils into the serosa and together with splanchnics "enter the stomach wall with the arteries, accompany their branches and are distributed to Auerbach's intra-muscular and to Meissner's submucous plexuses. Fibrils from the myenteric plexus extend to the *tunica muscularis* from the submucous plexus to the vascular wall and to the secreting epithelium. They transmit motor, vasomotor, secretory and sensory impulses." (2) This is the portion of the stomach that will receive the blunt of psychic trauma with the resultant hypermotility, hypersecretion, hyperechlorhydria, hypertonicity and vascular spasm.

If we had no information about the pathology of "peptic" ulcer other than this unique site-predilection, we might arrive at the following logical conclusion: The stomach contents can not play a deciding rôle in the etiology of "peptic" ulcer since the organ is a hollow viscus and its churning and contracting action would expose equally all surfaces of the stomach to the erosion of the hydrochloric acid, the digestion of pepsin or the physical trauma of sharp food particles. These are unable to damage over three fourths of the surface of the stomach which includes the greater curvature and most of the cardiac portion. There must be some physiological or structural difference in this small ulcer bearing area, in its musculature or vascular bed or innervation, peripheral or central, that plays the deciding rôle in ulcer formation.

### PATHOLOGY

First we might investigate the macroscopic and microscopic picture of the ulcer itself and see what light it may throw on its origin and development. The destructive process of a gastro-duodenal ulcer is *reversed* from that of the ordinary ulcer found in other body tissue. On cross-section we find that the greatest damage occurs near the serosa, in the muscularis and in the submuscularis, with astonishingly little destruction of the mucous membrane itself considering the chronicity of the lesion. (Figure 6) This

unusual reversal of the destructive process has been variously described by different pathologists. C. B. Morton (11) describes the cross section of many ulcers as the "crater is often cone-shaped with the apex toward mucosal surface" and "the submucosa is definitely, sometimes markedly, thickened having in section the shape of a wedge with the thick part pointing to the crater and the point gradually tapering off and losing itself in the normal submucosa, distal to ulcer" and conversely in the healing process. Bunting (17) says "repair of mucosa is faster than that of submucosa" so that "scars may be present in the serosa with or without adhesions, in the intramural structures with corresponding limitation in blood supply or in the mucosa". W. J. Stewart (11) speaks of the thickening and opacity of serosa as a result of fibrosis and edema". The opening is "often slit like owing to overhanging margins and... undermined edges". This evidence of maximal damage to the stomach wall structures furthest away from the mucous membrane shows that the stomach contents plays no part in initiating the lesion. If it did we would logically expect the greatest damage to be to the mucosa and nearby structures with lessening damage as we approached the serosa. The direct opposite is true. Obviously then, the origin of the destructive process must be sought outside of the stomach. Here again the pathological study helps to show the causative factor.

In nearly every "peptic" ulcer, if careful study is made especially beyond the ulcer bed some evidence of obliterative arterial disease may be found. Dr. Schutz (18) in examining thirty specimens of ulcer found arterial obstructive lesions in every case. Other observers have reported similar findings. (9,19) These thrombi so generally found in "peptic" ulcers serve as a key to its etiology. Such extensive and constant vascular occlusion must be on a basis of spasm. No embolic phenomena could duplicate this picture particularly in view of subsequent proof. Vascular spasm means faulty innervation or vegetative imbalance which takes us back to our personality study of the nervously unstable individual.

Vascular spasm and thrombosis mean a destructive process that is dry and clean, which is precisely what we find in "peptic" ulcers. The first thing about these gastro-duodenal ulcers that strikes the surgeon is their cleanliness. As Deaver (10) puts it they appear as if "punched out by a sharp instrument". (Figure 7.) There is little active inflammatory changes about the ulcer (19). They are clean bacteriologically as well as histopathologically. Smears and cultures are sterile (20).

This is equivalent to the effect of "dry gangrene" in any other part of the body. We are familiar with the sharp demarcation in Raynaud's gangrene. In the early stages when the ulcers occur on tips of dry, opaque and indurated fingers we find clean and sharply cut out defects and if these were exposed to constant washings as is the ulcer of the stomach we would find a replica of its microscopic picture. The pepsin and hydrochloric acid merely perform the physical part of cleaning the ulcer after it is formed but have *absolutely nothing* to do with its primary etiology. After all the gastric mucosa has lived in an acid medium for many millions of years and as might be expected has developed a biological resistance in this long trek of evolutionary development.

\*A paper on the "Classification of Peptic Ulcer" is in preparation.



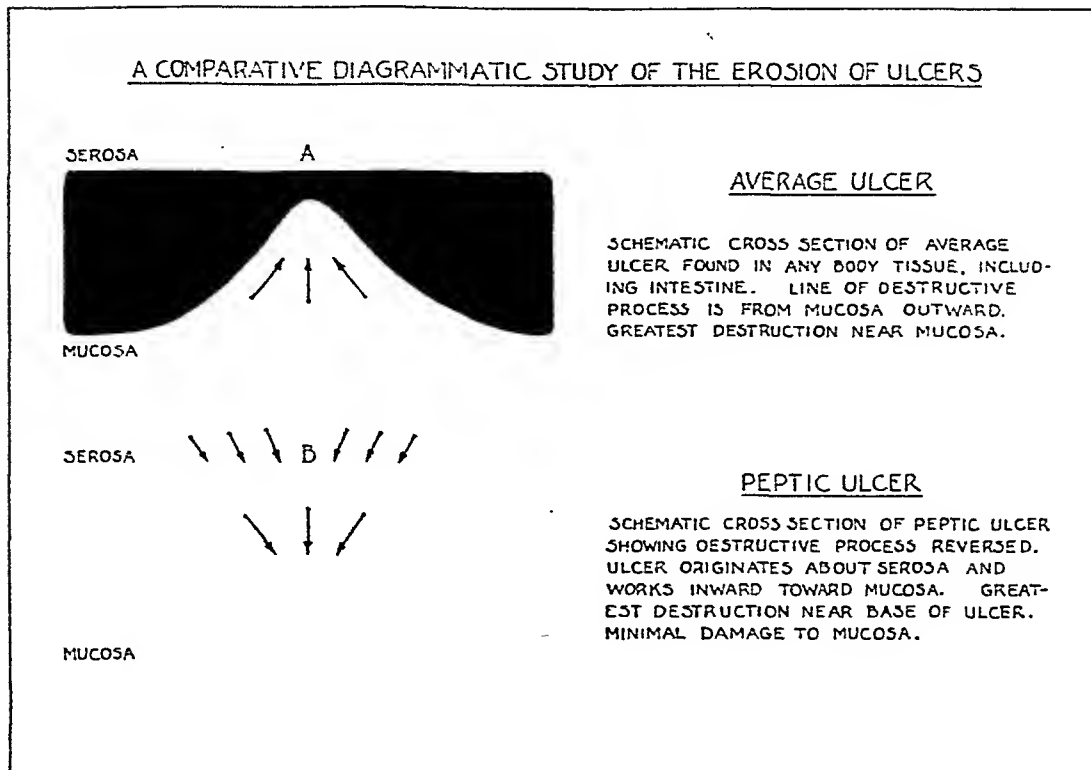


Fig. 6

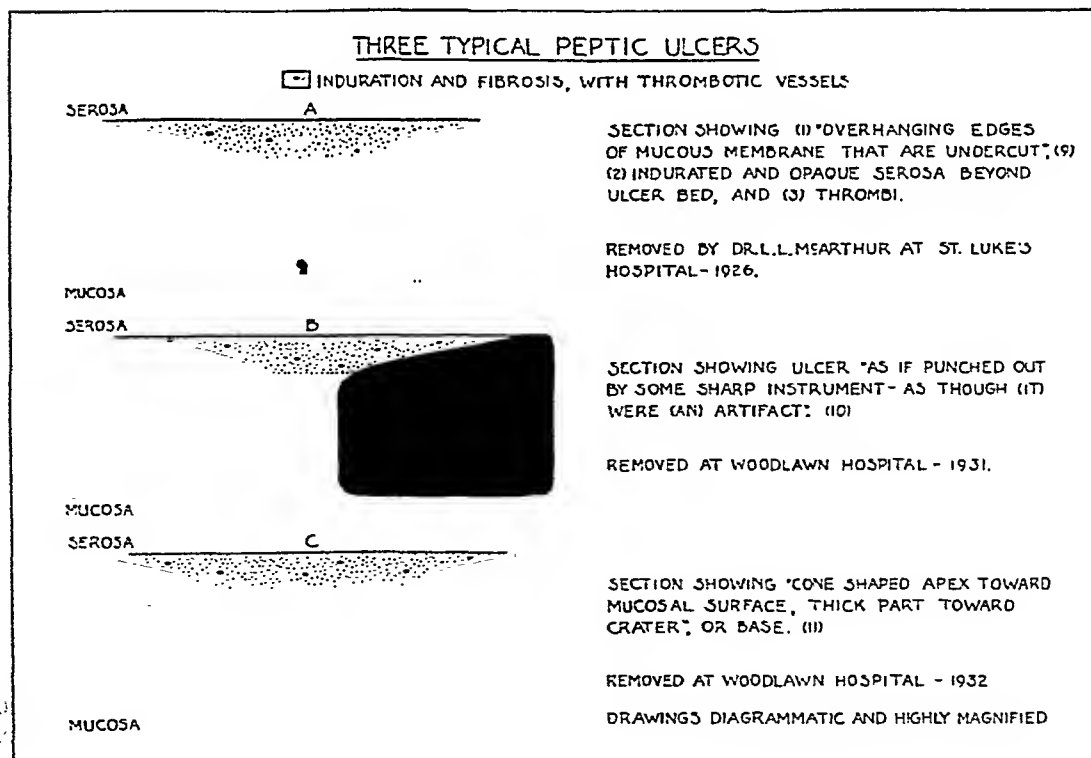


Fig. 7

Thrombosis is responsible for the induration and thickening of the serosa and subserosa. The tissue feels dead to the touch and shows a loss of normal translucency; this is easily visible at the operating table. Often after gastric resection the surgeon is greatly disappointed and surprised not to find any ulcer. The mucous membrane is intact throughout. But the site of trouble may be recognized in the opacity of the serosa with or without scarring which may extend to varying depths showing limited blood supply and thromboses. (17).

with those of "peptic" ulcer excepting for the niche. There is evidence of hypertonicity, hypermotility and hypercontractility of stomach, rapid emptying and deformity of duodenal bulb. The disease has the elements of chronicity together with periods of exacerbations followed by remissions. (22) They cannot be differentiated clinically from the true ulcer patients and to all intents and purposes are the same as far as course and response to therapy are concerned. (23) They differ from the ulcer patient only in the degree of extension of an identical pathological process. (24)

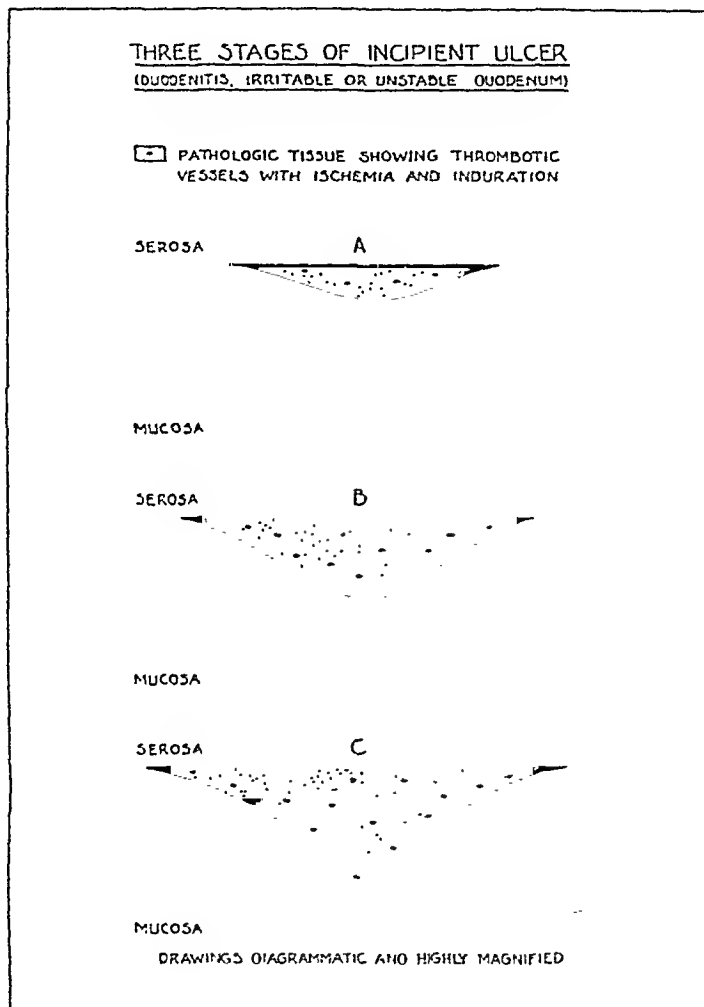


Fig. 8

### REVEALING STORY OF "DUODENITIS" AND INCIPIENT ULCER

We are familiar with the patient who has most of the symptoms of "peptic" ulcer but lacks the final verifying evidence of the niche in the X-ray film. After varying periods of therapy the patient may return for a second or even third X-ray and the niche may become discernible and a diagnosis of ulcer is made. These patients are of the same build discussed above, the male sex predominates 5 to 1, they show similar nervous instability and their distress comes on one or two hours after food and is relieved by alkalis or food. (21) They invariably have hyperchlorhydria and hypersecretion. The X-ray findings are identical

Pathologically we find the serosa thickened and indurated. The muscularis has some round cell infiltration, is edematous and looks pale and ischemic. The mucous membrane in most cases is entirely intact. Later as the process extends pin-point defects may be noticed in a few of the cases. (25) Some surgeons have had the rare opportunity of observing the causative mechanism at work.

"While operating on the stomach I have encountered particularly in the region of the ulcer-bearing area, pale almost white ischemic areas due to local spasm. The area of ischemia persisted for several minutes followed suddenly by a return of circulation. Still no ulcer could be detected. These are the individuals who

so frequently return within a few months after a futile exploratory operation, not only with outspoken symptoms but with definitely demonstrable X-ray signs of ulcer." (26).

They are "ulcer" patients without an ulcer, with an intact mucosa. In other words, the typical ulcer syndrome has been produced by a pathological process in the submucosal layers involving serosa, muscularis and intervening structures up to the mucous membrane. The erosion of the mucous membrane is not a necessary part of the pathology and the classical picture may be obtained without it.

Mental strain and anxiety have produced in these cases of incipient ulcer an imbalance of the vegetative nervous system about the lesser curvature and duodenum. This has led to spasm of the vessels in the serosa and muscularis but the circulatory impairment has not as yet extended to the mucous membrane. (Figure 8) With a temporary release of the individual's tension there is an arrest of this pathological physiology of vascular spasm, therefore it lacks the last stage in the production of a full bloomed "peptic" ulcer. There is enough ischemic pathology in the stomach wall, submucosal structures and "hyper" physiology generally to give the classic syndrome of "peptic" ulcer. (27).

It is clear that hydrochloric acid or pepsin or local trauma could not have initiated the lesion in view of the existence of a normal mucous membrane. Even the most enthusiastic advocates of these theories would not suggest that there possibly could be penetration into the stomach wall through an intact mucosa. The acid of the stomach could not produce the pain since the intact mucous membrane serves as an effective barrier covering the diseased tissue underneath. The rôle of hyperacidity in the ulcer syndrome becomes clear. Here then is a disease of psychogenic origin in which nervous stimuli rain down upon a small portion of the gastro-intestinal tract. The results are enhanced physiological functions mediated by these nerves, *viz.* hypermotility, hypersecretion, hyperchlorhydria and hypertonicity of vascular bed leading to spasm. The increased acidity is an associated finding just as much as leucocytosis is in most infectious diseases. And it would be as idle to focus one's attention on the leucocytosis instead of the invading organism as it is to regard hyperacidity as the *sine qua non* (28) of ulcer and rest content with its neutralization.

#### PSYCHOGENIC FACTORS IN DUODENAL ULCER

Dr. Harvey Cushing describes in his penetrating article (29) how his interest was aroused in the relationship of the brain to "peptic" ulcers. A patient died rather suddenly following an operation for brain tumor and autopsy revealed a perforated "peptic" ulcer. This has had corroborative support from other brain surgeons. Also certain brain tumors are occasionally associated with ulcer of the stomach or duodenum.

Beattie (29) has shown that electrical stimulation of tuberal centers causes increased motility of stomach, hypersecretion and ulceration near the lesser curvature.

Ulcers have been produced by injecting pilocarpine and physostigmine in the experimental animal over a long period of time. These drugs stimulate the parasympathetic system. We know that the interbrain is

the seat of the primitive nervous system and probably of a parasympathetic center.

These are four experiments entirely objective in their scope pointing to the relation of the interbrain to "peptic" ulcer. Let us now turn to the clinical picture which is even more convincing and which embodies the emotional and subjective content of the individual.

#### CASE REPORTS

Case IV. Mr. L. P. A. age thirty-one, who developed a duodenal ulcer under heavy financial responsibility, ill for two months in spite of management, decides to go to the North Woods. Here on irregular meals of a guide's cooking of flapjack and hard tack, with exposure to wet and cold and doing hard work he becomes symptom free in two days. He returns to Chicago and within two weeks suffers an exacerbation of ulcer symptoms.

Case X. Mr. E. C. N. (personal communication Dr. J. A. Hutton) Newspaper reporter with a duodenal ulcer develops symptom when on a specially heavy assignment. Advised to take capsules containing phenobarbital and atropine several days before and during assignments and now is able to complete his work, relatively symptom free.

Case XI. Physician age fifty-two. Gastro-enterostomy in 1915 for duodenal ulcer. Perfect health until June 1932 when he killed a man with his automobile. He bled one month later. X-ray showed deformed duodenal cap. Operation September 22nd showed duodenal ulcer (6).

These case histories show the direct relationship of mental strain and anxiety in the production of "peptic" ulcer (30). They further show that the removal of the mental strain resulted in symptomatic cure. These cures (and numerous others could be cited if space permitted) were accomplished without interfering with acidity, diet or focal infection. Merely a release from mental strain and this alone was necessary to bring about symptomatic cure.

These clinical observations, to which nearly every physician can testify, contain much of the kernel of the ulcer problem with its far flung ramifications into heredity, constitutional and personal selectivity and the emotional and vegetative imbalance.\* These clinical observations of the cause and effect relationship between mental strain and "peptic" ulcer show the need for a shift of emphasis from the ulcer itself and the interior of the stomach to the interior of the cranium.

In the final analysis, the determining factor of the course of this pathological physiology is the individual with his inherited neuro-psychological equipment in interaction with his environment. Whether the disturbing environment stirs up a dyspepsia of hypertonicity and hyperchlorhydria for a few days or a week; or whether it develops an incipient "ulcer" or "duodenitis"; or actually produces ulceration, hemorrhage or perforation; whatever their final result these processes all have this in common:—a direct circuit from the brain to stomach or duodenum. The bombardment of stimuli against the richly innervated lesser curvature and duodenum has as much crushing effect in its bloodlessness as the constant stimulation of the vegetative system has in producing gangrene in the fingers in Raynaud's disease, gangrene in the legs in the thrombo-angiitis-obliterans, and somatic

\*The sympathetic and parasympathetic systems have been omitted deliberately in this paper. Their respective inhibitory and excitatory fibers and their cortical relationships have not been worked out as yet. There is even definite proof of some cerebral control of visceral function. However, the clinical application of their combined interaction can proceed just as well until the whole subject is more fully elucidated. (31)

destruction in trophic ulcer. (30) The identical process stops the heart in coronary spasm and thrombosis and renders the kidney tissue impotent in nephrosclerosis. (32).

We are now on the verge of a fuller comprehension of the extensive damage inflicted on viscera by psychic trauma. It is natural that this source of pathology should be one of the last to be unfolded. We would, of course, in the onward progress of medicine, first study the objective manifestations of disease, *e.g.*, fracture, physical trauma, infectious diseases, tumors, endocrines, etc. Considerable advance has been made in these fields and we now should be prepared to study the effect of "emotional conflicts which are breaking down physical tissues."

### CONCLUSIONS

1. "Peptic" ulcer is shown to possess the following *unique selectivity* which is unusual in the annals of medicine.

#### (a) Racial Selectivity.

The animal kingdom does not develop "peptic" ulcer. The negro and lesser pigmented races are immune to the disease. The white race alone is susceptible.

#### (b) Anthropometric Selectivity.

Only the long thin individual of the white race is susceptible. No lateral build individual was found in this series of 70 cases.

#### (c) Personality Selectivity.

Most ulcer patients show some nervous instability especially undue anxiety, fear and worry.

#### (d) Sex Selectivity.

The male sex is predominantly susceptible, 6 to 1 in this series of 70 ulcer cases. The few females that develop ulcer often show some masculine traits.

#### (e) Site selectivity.

Only about 4 inches of the lesser curvature of the stomach and the first inch of duodenum develop "peptic" ulcer.

2. *Pathological Uniqueness.* It is shown that a cross-section of a "peptic" ulcer shows maximal damage to layers near serosa and minimal damage to mucous membrane. This is a reversal of ulcer destruction elsewhere. Thrombi are present and the erosion is clean histologically and bacteriologically. This must mean vascular spasm due to vegetative nervous imbalance leading to thromboses, ischemia, necrosis and ultimate ulceration.

3. *Incipient Ulcer.* This has further confirmation in the X-ray study and surgical observation of incipient ulcer. The ulcer syndrome is shown to exist

without ulceration of mucosa. The pathology is intramural or in the submucosal tissue. This proves that the destructive process arises from without the stomach, from above downwards and that the stomach contents including hyperacidity have *absolutely nothing* to do with the primary etiology of "peptic" ulcer.

4. Operations on the brain have produced "peptic" ulcers. Electrical stimulation in the region of the basal ganglia and tumors in the interbrain have also caused "peptic" ulcers.

5. Finally case histories are presented showing that mental strain, anxiety and fear are the deciding factors in the exacerbation of symptoms and release from them are shown to result in symptomatic cure.

The psychogenic theory, alone, explains all of these unique features of "peptic" ulcer. The lesion is limited to the lesser curvature of the stomach and duodenum because this region is richest in vegetative nerve supply. The pathological picture of thrombosis and a clean cut out lesion are due to vascular spasm following stimulation of the vegetative system. Only the long thin individual who is given to worry and fears is susceptible. It is common knowledge that the lateral type or short and stocky individual is easy going and less inclined to worry. He is too jovial to upset his gastro-intestinal innervation, so he seldom if ever develops a "peptic" ulcer. The pure blooded negro is practically immune to the disease although he eats the same food and is subjected to the same "focal infection" as the white man. Why does this disease skip an entire race? The answer is an anthropological one based on hereditary differences of psychological structure and function. The negro race in its evolutionary ascent has not, as yet, acquired the habit of worry so peculiar to the white race under pressure of routine civilized living. The negro meets life's frustration with greater calm and equanimity—sometimes even with laughter.

### SUMMARY

This paper advances the psychogenic theory of "peptic" ulcer. It claims that this disease is found only among susceptible individuals of the white race—usually the long thin type who are given to worry and nervous instability. These individuals with their fears and anxieties develop an imbalance of the vegetative nervous system. This results in a bombardment of stimuli to the lesser curvature of the stomach and duodenum producing vascular spasm, thrombosis, induration, ischemia, and finally necrosis and ulceration.

### REFERENCES

1. Karsinow, R.: *J. A. M. A.*, Nov. 18, 1933, p. 1608.
2. Carey, E. J.: *Brit. Medical Journal*, Vol. XXX, No. 7, July 1931 *Am. Jour. Surg.*, W. C. Alvarez, Vol. 18 No. 2, p. 207, Nov. 1932; Personal Communication Dr. R. H. Jaffe.
3. Rivers, A. B.: *Arch. of Int. Med.*, Jan. 1934, Vol. 53.
4. Keen, *Surgery*, Phil., 1921, Vol. 4, p. 1142.
5. Bergsma, S.: *Arch. Int. Med.*, Jan. 31.
6. Hartman, H. R.: *Med. Clinics of N. A.*, May 1933, p. 1357; *Neurogenic Factor in Peptic Ulcer*.
7. Harris, S.: *J. A. M. A.*, Nov. 10, 1928 p. 1462.
8. Chace, A. F.: *Am. Jour. Dig. Dis. and Nutrit.*, Vol. 1, No. 12, p. 565.
9. Stewart, M. J.: *Int. Clinica*, 4:1-23 and 4:14-23.
10. Deaver, J. B. and Holman, S. P.: *Am. Jour. Surg.*, Oct. 1927, p. 333.
11. Morton, B.: Observation on Peptic ulcer, *Ann. Surg.*, Feb. 1927.
12. Draper, George: *Digestive and the Man*. The Macmillan Co., 1930.
13. Constitution and the Man.
14. (3) Man-Environment Unit and Peptic Ulcer. *Arch. Int. Med.*, April 1932.
15. Hartman, H. R.: *The Med. Clinics of North America*, Vol. 13, No. 6, p. 1259.
16. Smithies, Frank: *Am. Jour. Med. Sci.*, 186:781, 1923.
17. Holmes and Hampton: *New Eng. Jour. of Med.*, May 11, 1933.
18. Jaffe, R. H.: *Chic. Med. So. Bul.*, p. 369, 1933.
19. Eusterman, G. B.: *Med. Clinic of N. A.*, Nov. 1930, p. 565.
20. Crohn, B. B.: *Affections of the Stomach*, Saunders, 1927, p. 547.
21. Bunting, C. H.: *Pathology of Gastro-intestinal ulcer*, *Wm. Med. Jour.*, p. 538, July 1931.
22. Schutz, C. H.: *Etiology of Gastric and Duodenal Ulcers*, *J. A. M. A.*, June 27, 1931.
23. Delafeld and Prudden, *Text Book of Pathology*, Wm. Wood & Co., 1922.
24. Trout, H. H.: *J. A. M. A.*, Vol. 104, No. 1, p. 7.
25. Miller, T. G.: *Med. Clinics of N. A.*, Jan. 1931, p. 811.
26. Kellogg, E. L.: *The Duodenum*, N. Y.
27. Rivers, A. B.: *Neb. St. Med. Jour.*, Nov. 1932, Vol. XVII, No. 11, p. 465.
28. Rivers and Dry: *Am. Jour. of Dig. Dis. and Nutrit.*, Vol. 1, No. 7, p. 523.
29. Judd, E. S.: *Path. Condition of the Duodenum*, *Lancet*, 4:216, April 15, 1921.
30. Judd, E. S., and Narel, G. W.: *Ann. Surg.*, 85, 386-390, March, 1927.
31. Held, L. W. and Allen, A.: *Med. Clinic of N. A.*, 1931, p. 819.
32. Meyer, Jacob: *Arch. Int. Med.*, Nov. 30, 1930.
33. Palmer, W. L.: *J. A. M. A.*, Vol. 101, No. 21, p. 1684.
34. Cushing: *S. G. O.*, July 1932, Vol. 55, 1-34.

30. Simpson, V. E.: *Ky. St. Med. Jour.*, March 1928.  
 Russ, W. B.: *J. A. M. A.*, Nov. 28, 1931.  
 Todd: *Behavior Patterns of the Elementary Tract*, 1930.  
 Eggleston, E. L.: *J. A. M. A.*, Vol. 103, No. 26, p. 2011.  
 Crohn, B. B.: *Am. Jour. Dig. Dis. and Nutrit.*, 1924, p. 773.  
 Crile: *Diseases Peculiar to Civilized Man*.  
 31. Ivy, A. C.: *Am. Jour. Dig. Dis. and Nutrit.*, 1934, p. 845.  
 Kiss, F.: *Jour. Anat.*, London, 66, 488, 1932.  
 McSwiney, B. A., and Spurrell, W. R.: *The Jour. of Physiol.*, Vol. LXXVII, No. 4, March 15, 1933.  
 Durante, L.: *The Trophic Element in the Origin of Gastric Ulcer*, *S. G. O.*, 22:399, 1916.  
 Mayo, C. H.: 1928 Atlanta Proceedings of the Inter State Post graduate Medical Assembly of N. A., p. 538-41.  
 32. Jaffe, R. H.: *Pathological Conference, Chi. Med. Soc.*, March 15th 1935, p. 549, *Ibid.*, p. 167, 1934.  
 36. Pribram, B. O.: *Klin. Wehnscher*, 2, 2112, 1923.  
 38. Schiassi, B.: *Ann. Surg.*, May 1925.

## A Follow-up of Ulcerative Colitis (Non-specific)\*

By

BURRILL B. CROHN, M.D.,

and

BERNARD D. ROSENAK, M.D.

NEW YORK CITY, NEW YORK

THE treatment and care of a case of non-specific ulcerative colitis usually are administered in an atmosphere of pessimism and doubt. The gallery of interested physicians expects the worst, hesitate to believe relief or restitution to health possible and surely expect one or more recurrences should the patient escape an immediate catastrophic. True, not without reason did the earlier clinicians call this disease *colitis gravis*: the severity of the symptoms, the progressive emaciation and anemia, the dehydrating and the exhausting diarrhea, protracted chronic clinical course and its disheartening recurrence might well earn for such a malady this dreaded opprobrium. Should the patient benefit by a therapeutic attempt or by one of nature's surprisingly frequent last-hour reprieves, it is usually held that the "cure" really is only a remission and that the "recurrence" cannot be far ahead.

All of which is unfortunately only too true. Twenty-five years ago, when cases of colitis were few and far between (?) and constituted "rare" cases of unusual difficulty as problems in therapeutics, the gravity of the prognosis was correctly assessed. But today, when through some mechanism which has not yet been explained, cases of colitis are common and familiar, with greater experience, increasing knowledge and a certain modicum of success, the self-confidence of achievement becomes established in the profession. Today, colitis is not a hopeless problem; we feel that we cure a fair, if not a fairly high, percentage of our cases, and what is more, keep them well. This note of optimism is well warranted by the facts; as the years roll on, the individual follow-up of each clinician grows with his maturity. This present generation of clinicians, and particularly gastroenterologists, is the first generation to apply itself intently to the problem of the etiology and therapy of non-specific ulcerative colitis; therefore this generation is the first one, which, having grown up with the problem, is now beginning to approach that stage where follow-up statistics and prognostic generalizations take shape and have real significance.

On this subject, very few statistical reports have been registered in medical literature. The vast experience of the members of the staff of the Mayo Clinic has been ably reported by Bargen (1) and lends a real tone of optimism not sufficiently recognized and appreciated by the profession and the public.

Some years ago we (BBC) reported a careful study

of cases of gastric and duodenal ulcer seen and followed over a course of 5 to 10 years; the cases reported were hospital-ward and clinic cases, culled from the working classes where the best means of treatment and the most conscientious follow-up were not always possible. Shortly after, Friedenwald published identical experiences with private patients under better hygienic and economic conditions. It was felt that the far better results reported by him, and the greater durability of his cures may have been due, in part, to the better social and financial condition of his patients, and to the privilege accorded these patients of being treated and followed over a long period by one man only, and that man one of vast experience.

### MATERIAL STUDIED

The following statistical follow-up of ulcerative colitis is, therefore, based upon 90 cases seen in "private practice". That does not necessarily imply that the patients were drawn from the luxury classes; on the contrary, they represent all strata of society. But they had the advantage of consistent treatment by one person, carried through to a successful or unsuccessful ending, and they had the will and the means to carry out the therapeutic directions and the dietary management which are requisite to the therapy of this disease. From this group of 90 cases, carefully studied and consistently followed from 2 to 14 years, some important facts regarding methods of treatment and the results of prolonged therapy logically may be deduced.

The age and sex distribution in this group differs in no wise from that published by many other authors when such facts have been drawn from far larger series of patients. The disease essentially is one of young adult life, both sexes being approximately evenly affected. The largest group falls in the third decade, the next largest in the fourth decade (Table I);

TABLE I  
Age and Sex Incidence

|                                                           |          |          |          |         |         |          |
|-----------------------------------------------------------|----------|----------|----------|---------|---------|----------|
| <b>Sexes:</b>                                             |          |          |          |         |         |          |
| Males                                                     | .....    | .....    | .....    | .....   | .....   | 43 cases |
| Females                                                   | .....    | .....    | .....    | .....   | .....   | 47 cases |
| Total                                                     | .....    | .....    | .....    | .....   | .....   | 90 cases |
| <b>Age Incidence, base of 87 ages:</b>                    |          |          |          |         |         |          |
| <b>1. Age groups:</b>                                     |          |          |          |         |         |          |
| 3-10                                                      | 11-20    | 21-30    | 31-40    | 41-50   | Over 50 |          |
| 5 cases                                                   | 12 cases | 36 cases | 23 cases | 7 cases | 4 cases |          |
| <b>2. Age limits:</b> 3 years to 58 years.                |          |          |          |         |         |          |
| <b>3. Average age</b> 29.1 years.                         |          |          |          |         |         |          |
| <b>4. 58 cases or 67% between 20 and 40 years of age.</b> |          |          |          |         |         |          |

\*From the Division of Medicine, Mount Sinai Hospital.  
 Submitted May 31, 1935.

the youngest in this group was 3 years, the oldest 58 years. Nearly always in young persons, (frequently the recent bride or the vigorous youth in his college years, or a young husband and provider) the disease takes toll of youth in its best period.

Of these 90 cases, we have records to date in 75 cases, constituting an 83% follow-up. These cases all have been seen or contacted personally in recent months. Occasionally, we accepted the report of the original physician regarding the present status of the case. Of the 75 cases, we can say with truthful assurance that 33 cases (44.5%) are cured. By "cured" we mean persistent cessation from symptoms and complete restitution to the normal. Again, 23 cases (30%) are regarded as improved. These patients retained their normal weight. Some of them were having at the most two to three soft bowel movements per day, but had no blood or mucus in the stools. They all had returned to their former activities and were in good general health. Others in this group suffered from mild intermittent recurrences of symptoms with intervening periods during which they were absolutely free of diarrhea. Eight cases, (10.9%) were unimproved, which means, to all practical purposes, invalidism. Eleven cases had died (Table II). These statistics will

TABLE II  
Follow-Up—2 to 14 Years  
(Ulcerative Colitis)

|                                  |                 |
|----------------------------------|-----------------|
| Total number of cases            | 90              |
| Number of cases followed to date | 75              |
| Per cent of cases followed       | 83%             |
| Analysis of cases followed:      |                 |
| Cured                            | 33 cases 44.5%) |
| Improved                         | 23 cases 29.9%) |
| Unimproved                       | 8 cases 10.9%)  |
| Deceased                         | 11 cases 14.8%) |
| Totals                           | 75 cases 99.9%  |

be discussed in greater detail in the course of the text. Suffice it to say that of the entire group, 75% are cured or improved and restored to efficiency.

Approximately half of the cases had been ill less than a year, thus constituting the treatment of the disease in what practically is a sub-acute or beginning chronic state. (Table III). The other half had been ill for from two to fourteen years, a fact which dem-

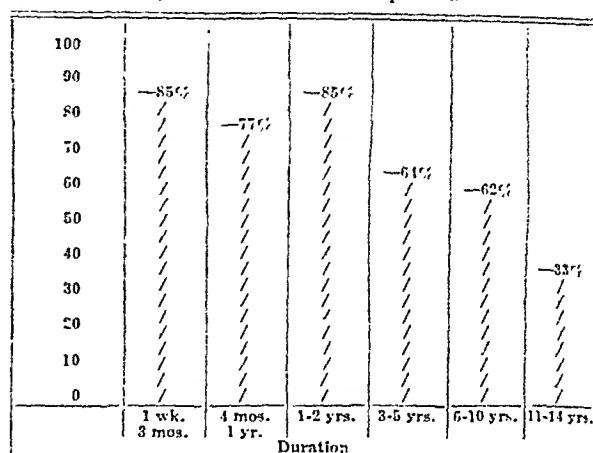
TABLE III  
Duration of the Disease When First Seen

| Duration       | Number of cases |
|----------------|-----------------|
| 1 wk. to 3 mo. | 15              |
| 4 mo. to 1 yr. | 29              |
| 1 to 2 yrs.    | 14              |
| 2 to 3 yrs.    | 14              |
| 4 to 10 yrs.   | 9               |
| 10 to 14 yrs.  | 4               |

onstrates the chronicity and the prolonged course characteristic for this malady. One point of interest becomes obvious, and that is that the percentage of cured and improved patients is maintained at a high level, even with the passing of time, providing treatment is begun within the first two years of illness. From this point on, the greater the duration of previous illness, the less likelihood of cure (See Chart A).

CHART A

Showing the Relation of Duration of Symptoms to the Per Cent of Cases Cured or Improved



Because the patient has been semi-invalided and ill for many years does not mean that the possibility of successful cure thereby is excluded. On the contrary, some of the most gratifying results were observed in just this class of long-suffering patient.

That the results are durable is to be seen when one analyzes the percentage of cured and improved cases seen in the course of the gradually increasing period of follow-up observation (Table IV). Over 70% of the cases are cured or improved in the first two and the first four-year periods. If relapses were common, we should expect to find a much smaller percentage of cure at the end of six or ten or fourteen years of follow-up. This is not the case, because, while the numbers followed have been much smaller as the years progressed, in the cases followed between six and fourteen years, the percentage cured is maintained. Table IV is very significant. For example, in a six to ten-year period of follow-up, there are fifteen cases, of which seven cases have been and have remained cured, six to ten years after the initial treatment without relapse. Add to that group, four cases that are so improved as to be regarded as restored to efficiency and ambulatory health and we are much gratified to observe the favorable outcome of therapy, even when observed over so long a period.

Two cases are known to be cured without relapse, and two cases are markedly improved when observed

TABLE IV  
"Cure" and Long Period Follow-Up

| Follow-up period:  | Total Cases | Long Period Results: |          |            |          |
|--------------------|-------------|----------------------|----------|------------|----------|
|                    |             | Cured                | Improved | Unimproved | Deceased |
| 6 mos. to 2 yrs.   | 23          | 11                   | 9        | 6          | 2        |
| 2 yrs. to 4 yrs.   | 21          | 10                   | 6        | 1          | 4        |
| 4 yrs. to 6 yrs.   | 6           | 3                    | 2        |            |          |
| 6 yrs. to 10 yrs.  | 15          | 7                    | 4        | 1          | 3        |
| 10 yrs. to 14 yrs. | 6           | 2                    | 2        |            | 2        |
| Total Cases        | 75          | 23                   | 23       | 8          | 11       |



over a period of from ten to fourteen years. These cures were affected not alone on mild cases, but on some of the most severe cases, most of which had been sick and invalided for from six months to six years before coming under our management, some of them having previously had as many as four or more recurrences.

#### THE EFFICACY OF THE VARIOUS TYPES OF THERAPY

Certain general rules of treatment were followed in all cases. *Retention enemas* of neutral acriflavin, in the strength of 1 to 4000 parts of normal saline solution, were employed as a daily routine. In the earlier years, before the use of intravenous medication, this represented, together with dietary regulations the sole therapeutic procedure. Very good results often were seen with this method when exclusively employed. When retention enemas created more irritation than relief, where a mucoid or catarrhal irritation resulted from their use, they were promptly discontinued. In general however, retention enemas rather than colonic irrigations gave relief and were welcomed by the patient. For several hours after the institution of such an enema the patient usually felt more comfortable and the number of stools was materially reduced. These retention enemas therefore were usually given in the evening in order to assure a better night's rest.

The *diet* in all cases was a liberal one representing all classes of foods, including all classes of vitamins, the main principle being the exclusion of roughage and such articles of diet containing substances likely to irritate the colon. When excessive diarrhea was present, deodorized tincture of opium was employed. The amount of opium was always restricted to the minimal dose which would just reduce the degree of anal irritation from the constant intestinal flux, and which would allow the patient sleep and rest between movements but without inducing constipation. To constipate a colitis case is to make him most uncomfortable. The common use of large doses of opium is deleterious, inducing cramps if continued, borborygmi and the conscious feeling of pent-up or imprisoned gas. A very practical way of administering opium is to give ten minims of deodorized tincture of opium after every alternate stool during the severe stage only. The administration of the drug is thus automatically regulated by the discharges: the more stools, the more opium, the fewer stools, the less medication.

Since 1921, following the suggestion of Arthur Hurst (2), of London, we have employed the *intravenous injection of polyvalent anti-dysentery serum*; this, regardless of whether dysentery organisms or phage or agglutinins were or were not present in the patient's blood. The patient was tested for serum sensitiveness by the intradermal or conjunctival method, (serum diluted ten times in saline) and then received a preliminary dose of 5 c.c. of serum intramuscularly. If no severe reaction followed, the patient received, every other day, an intravenous dose of serum varying from 5, 10 or 15, to 20 c.c., the dose depending on the degree of reaction. A severe febrile reaction was welcomed. A certain degree of anaphylactic shock was regarded as more beneficial than deleterious. The most beneficial results were seen in those patients in whom the intravenous injection of serum resulted in immediate serum shock analogous to a non-specific protein reaction and in those who showed late serum sickness with urticaria and even joint manifestations.

The use of polyvalent anti-dysentery serum seemed to give us best results. (Table V).

In order to determine whether the effect of this serum was a specific or a non-specific one, we attempted, in a number of cases, to duplicate the results by the intravenous injection of typhoid vaccine, such representing a convenient and direct method of non-specific protein therapy. Some fairly good results were seen (Table V). Other miscellaneous methods of treatment were tried at various times in the course of years, these methods including autogenous vaccines of fecal organisms, Bagen's serum and vaccine, transfusions, etc., some with good results, many of them without any noticeable effect. It would seem that among the various types of intravenous therapy, no one item seemed to have a specific effect upon the

TABLE V  
Relationship of Therapy to Present Condition:  
MEDICAL CASES

| Basic Therapeutic                      |  | Number of Cases: |          |            |          |
|----------------------------------------|--|------------------|----------|------------|----------|
| Procedure:                             |  | Cured            | Improved | Unimproved | Deceased |
| Retention enemas<br>Neutral Acriflavin |  | 9                | 5        | 2          | 3        |
| Polyvalent Anti-Dysentery Serum        |  | 16               | 6        | 3          | 3        |
| Intravenous Typhoid Vaccine            |  | 2                | 3        | 1          |          |
| Miscellaneous*                         |  | 4                | 2        | 1          | 1        |
| SURGICAL CASES                         |  |                  |          |            |          |
| Procedure:                             |  |                  |          |            |          |
| Ileostomy                              |  |                  | 5        | 1          | 3        |
| Partial Colectomy                      |  | 2                | 2        |            |          |
| Ileosigmoidostomy                      |  |                  |          |            | 1        |
| Totals                                 |  | 33               | 23       | 8          | 11       |

\*Autogenous vaccines, Bagen's serum, transfusions, routine diet and medication only.

disease. It soon became obvious that any protein agent which would produce a protein shock and a febrile reaction, could bring about a beneficial change in the chronic course of this disease. The change from the slow, lethargic chronicity into a sudden flare-up induced by the protein therapy of whatever type, frequently seemed to alter the long drawn-out course of the malady. After several severe protein shocks, the temperature would frequently subside, diarrhea gradually and more slowly diminish until constipation was achieved and the general health of the patient, appetite, strength and weight began to show steady improvement. This experience of ours in observing the beneficial effect of protein shock was substantiated by remarks of other observers using still more varied means of therapy. Those using Bagen's serum and Bagen, himself, have observed that the best results were seen where the serum created severe protein shock, indicating that the serum acted as a non-specific protein as well as a specific antitoxic agent. The same may be said of transfusions.

Kantor, (3) using repeated small transfusions, has seen a general gain of hemoglobin and well-being; his

best results (as were ours) were observed when the transfusion was definitely accompanied by a febrile reaction. The experience of Andresen (4), with mercurochrome employed intravenously, was analagous. Here again the best results were seen in those cases exhibiting the greatest reaction to the intravenous therapy.

Our personal experience convinced us of the superiority of the use of polyvalent anti-dysentery serum. Whether the disease is an attenuated dysentery, a mild endemic dysentery or not, whether agglutinins were or were not present in the patient's blood, splendid results followed the specific serum method of treatment. In certain cases, it would appear almost as if the anti-body content of the serum were an important factor, particularly when high agglutinin *titers* were found in the blood of the patient. At other times, when no agglutinins were present, the serum still acted in a most prompt and efficient manner. Not alone does it constitute an excellent non-specific protein, but in its late production of serum-sickness, with urticaria and fever, it seems to act in its very best manner upon the course of the disease. This observation has also been made by Kalk (5), who used simple horse serum for the treatment of ulcerative colitis. His best results were seen in those patients showing the most serious instances of serum sickness.

The mortality of the disease under medical treatment was 11% (8 cases), these cases representing deaths from inanition, gradual exhaustion, anemia complicated by nutritional edema, and an occasional rare case by perforation or by gross hemorrhage; three additional cases died as a result of surgical intervention. Under *surgical treatment*, we regard ileostomy, as do almost all other writers, as the operation of choice, but one which should be restricted only to cases which are regarded as incurable under any form of medical therapy. We realize, that when an ileostomy is performed, the life of the patient may be saved, but that the disease thereby is stamped and

sealed as an incurable illness. In the course of years sigmoidoscopic study of cases of ileostomy shows an unhealed and unhealing mucosa, characterized by deep ulcerations, polypoid transformations, strictures and occasional malignant degenerations of the polys which are present. Only colectomy is indicated, once an ileostomy is performed. Our experience, however, with total colectomy, is insufficient to warrant discussion at this moment. Partial colectomy for localized forms of colitis have been very successful. The mortality of ileostomy, on the other hand, has been very high, not less than 33 1-3%; since however we restrict this operation to the most hopeless cases, one can expect a high mortality. The success of the Lahey Clinic (6) with partial extirpation of the colon and permanent ileostomy is one of the most promising chapters in the surgical treatment of this malign malady.

Our percentage of cured and improved is no better than those of Bergen (7) and his co-workers at the Mayo Clinic. Our follow-up period, for a fair proportion of our cases (6 to 14 years), is longer than those reported in Bergen's latest three-year follow-up. Though we may not accept the *diplostreptococcus* of Bergen as the proven cause of this disease, we have nothing but enthusiasm for his fine therapeutic results. If he, using a streptococcus vaccine and serum, obtains the approximate same percentage of cure as we do, using various means, but mainly anti-dysentery serum, it would all the more appear as if the disease yielded to various agencies, but always best to intravenous protein medication.

*Skillful neglect does not succeed with ulcerative colitis.* An active program and an experienced therapist are essential to terminate and cure those longstanding, chronic, insidious cases. Nature occasionally, unaided, will surprise one with a spontaneous cure. Unfortunately, nature is lax and undependable, but a strict and aggressive therapeutic program will bring to a favorable and permanent outcome a large percentage of supposedly incurable cases.

#### REFERENCES

1. Bergen, J.: Colon, Rectum and Anus. Rankin, Bergen and Buile, 1932.
2. Hurst, Arthur F.: *Guy's Hosp. Reports*, LXXXI-26, 1921.
3. Kantor, J.: *Am. Jour. Dig. Dis. and Nutr.*, 11-1, 1935.
4. Andresen, A. F. 1., and D'Albora, J. II.: *Trans. Amer. Gastroenterol. Assn.*, 1933:36.
5. Kalk, H.: *Zeit. F. Klin. Med.*, 180:560, 1931.
6. Cattell, R. B.: *J. A. M. A.*, Vol. 104-104, 1935.
7. Bergen, J.: *Trans. Amer. Gastro. Enterol. Assn.*, p. 53, 1933.

## The Acutely Ill, Jaundiced Patient: a Report of Twenty-one Instances of Hepatic Icterus, Seven of Whom Had High Blood Nitrogen\*

By

S. G. MEYERS, M.D., OSBORNE A. BRINES, M.D.

and

BENJAMIN JULIAR, M.D.

DETROIT, MICHIGAN

THE patient who is jaundiced but not acutely ill is one frequently met with in clinical medicine. Such a patient might be affected with catarrhal jaundice, carcinoma of the head of the pancreas, stone in the

common duct if complications are absent, or a variety of less common conditions.

The patient who is both jaundiced and acutely ill presents a different picture. The presence of jaundice in a patient who is acutely ill is ominous, death often occurring in a few days. The serious prognosis con-

\*From the Receiving Hospital and the Wayne University College of Medicine, Detroit.  
Submitted May 22, 1935.

sequent on this combination of symptoms makes rapid clinical orientation desirable. Liver damage of a severe degree usually is present; intensive treatment is necessary although in only a small percentage of these patients are the results of such treatment satisfactory.

### MATERIAL STUDIED

The data in this paper was compiled from the clinical and pathological records of twenty-one cases. These patients, acutely ill and with marked jaundice, were seen at the Detroit Receiving Hospital in the last seven years. The clinical and pathological records of a larger number of patients were studied where the jaundice was a minor sign of an overwhelming but obvious infection, but these cases are not being reported here. This paper is confined to observations where liver damage played an important or dominant rôle in the illness. Each case selected showed evidence of hepatic icterus; all cases of obstruction by malignancy, stone, etc., have been carefully excluded.

### CLINICAL OBSERVATIONS

The usual *clinical picture* encountered in these twenty-one cases corresponds with the textbook description of acute yellow atrophy. This syndrome also has been named "icterus gravis" and "the cholemic state" by various authors. Table I is a summary of the frequency of symptoms observed. Deep jaundice invariably was present. The icteric index ranged from 37 to 235. In more than half of the cases the icterus index was in excess of 100 at some stage of the disease. The serum bilirubin ranged from 312 to 22.1 mg. per 100 cc. Vomiting was the next most constant symptom occurring in about three-fourths of the group. Abdominal pain was present in 71 per cent and was due to abdominal distention from ascites, distention of the liver capsule or it was a severe, colicky pain resembling gall stone colic ("pseudo-gall stone colic"). Nervous symptoms particularly were common; evidence of mental disturbance was prominent early in twelve of the twenty-one individuals. The mental state was characterized as "markedly lethargic," "irrational," "delirious," "semi-stuporous" or "comatose." Epileptiform convulsions occurred in one patient. Bleeding occurred in five patients, two of whom had hematemesis, one purpurae, one epistaxis and one bleeding from the gums.

The *course* of the entire group was remarkable in that, once the acute symptoms had developed, death occurred in a relatively short time. The following figures illustrate this.

|                                                   |         |
|---------------------------------------------------|---------|
| Lived less than twenty-four hours after admission | 5 cases |
| Lived one to three days after admission           | 3 cases |
| Lived four to seven days after admission          | 7 cases |
| Lived eight to fourteen days after admission      | 2 cases |
| Lived fifteen to twenty-six days after admission  | 4 cases |

|       |          |
|-------|----------|
| Total | 21 cases |
|-------|----------|

The *life expectancy* with this illness fell into two groups: One group in which the entire course of the disease lasted from one day to several weeks; and a second group with a long history of liver disease, which finally terminated in icterus gravis shortly after hospitalization.

### PATHOLOGICAL DATA

A summary of the hepatic and renal pathology in our twenty-one cases of hepatic jaundice is shown in Table II. It will be seen that only ten of the twenty-one livers showed necrosis, the remaining eleven being

TABLE I

*Symptoms and Signs in 21 Cases of Hepatic Icterus*

|                          |          |              |
|--------------------------|----------|--------------|
| Jaundice                 | 21 cases | 100 per cent |
| Vomiting                 | 16 cases | 76 per cent  |
| Abdominal Pain           | 15 cases | 71 per cent  |
| Palpable Liver           | 10 cases | 48 per cent  |
| Contracted Liver         | 3 cases  | 14 per cent  |
| Liver Tenderness         | 8 cases  | 38 per cent  |
| Spleen Palpable          | 1 case   | 5 per cent   |
| Ascites                  | 7 cases  | 33 per cent  |
| Nervous and Mental Dist. | 12 cases | 57 per cent  |
| Bleeding                 | 5 cases  | 24 per cent  |
| Chills                   | 5 cases  | 24 per cent  |
| Fever                    | 15 cases | 71 per cent  |
| Leukocytosis             | 12 cases | 57 per cent  |

divided among cirrhosis, cloudy swelling and fatty liver. Only three of the twenty-one cases had definite renal pathology, two of whom had chronic focal nephritis and one had chronic glomerulonephritis. All had "bile nephrosis," characterized by pigmentation and cloudy swelling of the tubular epithelium.

### CLINICAL COMMENT

One case which showed a fatty liver without necrosis of the cells clinically could not be distinguished from the cases of liver necrosis, both having the clinical picture of icterus gravis, marked jaundice, vomiting and confused mentality. The fully developed picture of icterus gravis with vomiting, deep jaundice and delirium also was observed in a case which at autopsy showed merely cloudy swelling of the liver, no other lesions of the liver being found on post mortem examination. A second patient with cloudy swelling of the liver also died with icterus gravis, without a cause for the liver damage being apparent before death. Autopsy revealed an unresolved pneumonia, which definitely fixed this as an infectious hepatitis consequent upon lobar pneumonia. This patient illustrates the difficulty of differentiating idiopathic icterus gravis from icterus secondary to some undiscovered, overwhelming infection.

These patients illustrate that cloudy swelling and fatty liver may cause the clinical picture of icterus gravis indistinguishable in life from the same symptoms caused by actual necrosis of the liver cells. The identical picture of icterus gravis also can be evident when cirrhosis without necrosis of the liver cells is present. This occurred in eight members of this series where a long standing cirrhosis of the liver was present, its termination being with deep jaundice, vomiting, mental symptoms and hemorrhages. In these cases there was present an already seriously damaged liver; the acute hepatic insufficiency was precipitated by some undetermined factor such as an acute infection or alcohol poisoning. In some patients, the cir-

TABLE II

*Summary of Liver and Kidney Pathology in 21 Cases of Hepatic Jaundice*

| Liver                               | Cases | Kidney                                     |
|-------------------------------------|-------|--------------------------------------------|
| Cirrhosis, without necrosis         | 8     | Normal except bile nephrosis.              |
|                                     |       | 1 chr. focal nephritis, bile nephrosis.    |
| Cirrhosis, with necrosis            | 4     | 1 chr. glomerulonephritis, bile nephrosis. |
|                                     |       | 2 normal except bile nephrosis.            |
| Necrosis, without other liver path. | 6     | 6 with bile nephrosis.                     |
| Cloudy swelling                     | 2     | 1 chronic focal nephritis.                 |
|                                     |       | 1 with bile nephrosis.                     |
| Fatty liver                         | 1     | 1 with bile nephrosis.                     |
|                                     | 21    |                                            |

rhosis had given symptoms for months or years by enlargement of the liver and spleen and ascites. In others, the symptoms of cirrhosis of the liver were latent and the patients presented the clinical picture of idiopathic icterus gravis, but at post mortem the previously existing cirrhosis was discovered.

It is interesting that the symptoms and signs of acute yellow atrophy, well known and usually easily recognized, constitute a clinical and not a pathological entity. The identical group of symptoms was associated with such lesions as hepatic necrosis, hepatic cirrhosis without necrosis, cloudy swelling of the liver and fatty liver. The dominating factor in correlating the clinical and pathological data probably lies in the sphere of hepatic function, where the liver has ceased to function the characteristic syndrome appears, at times unassociated with microscopical evidence of hepatic necrosis.

Lepehne (1) gives an excellent summary of the etiological factors involved in icterus gravis. He states that icterus gravis can arise suddenly and without demonstrable cause, or it can arise from a known toxic agent such as chloroform, phosphorus, einchophen, alcohol, salvarsan; from some infection as syphilis or Weil's disease; from some metabolic change as in pregnancy, or as a terminal event in the presence of previous liver disease, as atrophic cirrhosis, biliary cirrhosis, etc.

The constant presence of icterus in these necrosis cases should not lead one to expect icterus in every case of hepatic necrosis, nor to dismiss the possibility of hepatic necrosis or insufficiency where jaundice is absent. We have encountered definite hepatic necrosis without jaundice in a case of marked thyrotoxicosis. Similar cases have been reported by Kerr and Rusk (2), Barker (3), and Beaver and Pemberton (4). Death, post-operatively, of patients with a cholelithiasis of long standing has been ascribed to "liver insufficiency" by Cave (5), Heyd (6), and Eiss (7). In these cases the jaundice may also be slight or absent, and the liver insufficiency may not be recognized clinically.

### ETIOLOGICAL FACTORS

There are so many possible etiologic factors in hepatic icterus that often it is difficult to choose which is the most likely. In one case, a choice could be made between syphilis, anti-syphilitic therapy and alcohol; in another, between alcohol, pregnancy and drug intoxication. An analysis of the twenty-one cases as to etiological and clinical features is reported in Table III. It is easy to overlook such important etiologic factors as an acute infection with masked or modified symptoms, or the ingestion of a drug the nature or significance of which the patient or doctor does not understand. Quite frequently these patients are mentally confused when first seen and an accurate history is not obtainable.

The differential diagnosis of hepatic icterus from that due to obstruction in one of the larger ducts is extremely important to the patient. An operation undertaken to relieve a wrongly diagnosed obstruction may cause death, the anaesthesia or shock of the operation being sufficient to push the poorly functioning liver over the brink into hepatic insufficiency. Patients with hepatic icterus are notably poor operative risks.

TABLE III  
*Etiological and Clinical Features*

|                                                                                                                                                                                | Cases |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| 1. Chloroform Poisoning (Sulcide).                                                                                                                                             | 1     |
| 2. Liver Necrosis during anti-leucet treatment. Probable arspenamine necrosis.                                                                                                 | 1     |
| 3. Idiopathic Acute Yellow Atrophy.                                                                                                                                            | 1     |
| 4. Clinical picture of "Catarrhal Jaundice" of unknown etiology, terminating with icterus gravis; acute yellow atrophy at autopsy.                                             | 2     |
| 5. Clinical picture of "Catarrhal Jaundice" of unknown etiology, then fresh rupture of gastric ulcer. Death 3 hours after operation. Subacute atrophy of liver at post mortem. | 1     |
| 6. Idiopathic acute hepatitis, death with picture of icterus gravis, only cloudy swelling of liver found at autopsy.                                                           | 1     |
| 7. Infectious hepatitis, giving clinical picture of icterus gravis, from a lobar pneumonia not recognized in life.                                                             | 1     |
| 8. Portal Cirrhosis, with previous alcoholic history, death with picture of icterus gravis.                                                                                    | 6     |
| 9. Portal Cirrhosis, no previous alcoholic history, death with picture of icterus gravis.                                                                                      | 2     |
| 10. Portal Cirrhosis, plus terminal infection                                                                                                                                  | 1     |
| (a) Abdominal abscesses                                                                                                                                                        | 1     |
| (b) Pancreatitis                                                                                                                                                               | 1     |
| 11. Hypertrophic Biliary cirrhosis, possibly associated with alcoholism or pregnancy. Death after operation to relieve possible biliary obstruction.                           | 1     |
| 12. Interstitial Hepatitis, death with picture of icterus gravis, possibly alcoholic in origin.                                                                                | 1     |
| 13. Syphilitic Hepatitis, death with picture of icterus gravis.                                                                                                                | 1     |
|                                                                                                                                                                                | 21    |

### ILLUSTRATIVE CASES

Case histories of patients illustrating some of the clinical pictures encountered follow:

1. *Chloroform Poisoning*, Case No. 11: A forty-eight year old attorney was admitted in coma following the drinking of chloroform. He became rational, but, two days after admission, jaundice, delirium, nausea and vomiting appeared, there was decrease in the size of the liver and the patient expired five days after admission. At autopsy necrosis of liver cells, predominantly at the center of the liver lobule, was found.

2. *Idiopathic acute yellow atrophy*, Case No. 1: A twenty-two year old boy was admitted, jaundiced and in coma. Five days before admission he had been taken ill with abdominal pain and had vomited blood. No history of previous illnesses, recent medication, alcoholism or other poisons could be obtained; loss of consciousness developed the day previous to admission. At autopsy acute yellow atrophy of the liver with diffuse necrosis of the liver cells was found.

3. *Previous picture of Catarrhal Jaundice*, termination with *Icterus Gravis*, Case No. 13: A fourteen-year old colored girl was admitted with the clinical picture of catarrhal jaundice of one week's duration. A previous history of pregnancy, operations for two breast abscesses and a right oophorectomy was given. On entrance the patient was well oriented and fairly comfortable altho' the conjunctivae were markedly icteric. Pulse and temperature were normal. The first week of her hospital stay was noted as "improving", "walking about the ward". On the eleventh day after admission, patient was noted as "dull and apathetic; sleeps during day"; on the fourteenth day "frequent vomiting, very toxic", on sixteenth day "temperature and pulse rising; vomiting pronounced, more deeply jaundiced." The patient finally became comatose and died, eighteen days after admission to hospital. Autopsy report showed extensive diffuse necrosis of liver cells.

4. *Portal Cirrhosis*, termination with *Icterus Gravis*, Case No. 8: A forty-two year old, white male, addicted to alcohol but who had discontinued its use eight months previous to final admission because of the development of ascites. He had previously been admitted to hospital, with a diagnosis of portal cirrhosis and had been tapped several times. A week before the final admission, ascites became

marked, jaundice appeared and gradually deepened and he began to vomit frequently. On admission he was very drowsy and intensely jaundiced. Ascites was present and the liver enlarged half way to umbilicus. The liver decreased in size to one finger breadth below costal margin before *exitus*. He vomited bile and later vomited blood. Patient expired five days after admission. *Autopsy* showed portal cirrhosis with recent necrosis of liver cells, apparently a moderately severe acute yellow atrophy.

5. *Infectious Hepatitis, simulating icterus gravis*, Case No. 4: A fifty-three year old white male, a heavy drinker of alcohol for past five years. Two weeks before admission chills and vomiting developed. His physician noted jaundice one week before admission; gradually the jaundice became deeper. On admission, lethargy, hiccup and deep jaundice were marked symptoms; herpes on lips, lungs apparently clear; liver indefinitely felt, three finger breadths below costal margin; temperature from 99° F. to 101° F.; white count 55,200 per cu. m.m., with 98 per cent polynuclear cells. The patient expired four days after admission. At *autopsy* there was an extensive unresolved pneumonia; the liver weighed two kilograms and showed cloudy swelling, and the kidneys showed chronic focal nephritis.

One explanation which suggests itself to account for the high non-protein nitrogen values is that it is due to an increase in the amino acid nitrogen. Thus, Rabinowitch (9) reported a case of acute yellow atrophy with extremely low blood sugar, blood urea of zero and a high amino acid nitrogen (216 mg. per 100 c.c.). Pathologically the liver cells practically were entirely absent, and the kidneys showed an acute degenerative nephritis with marked fatty degeneration of the tubules. The high non-protein nitrogen figures obtained in our seven cases cannot be due to low urea nitrogen and high amino acid nitrogen as can be observed in Table IV which shows that the urea nitrogen figures were also high.

Dehydration also does not explain satisfactorily the rise in the non-protein nitrogen as figures over 60 mg. per 100 c.c. are unusual in dehydration. Certainly the four cases in which the non-protein nitrogen was over 100 mg. per 100 c.c. cannot be explained on this basis.

Alkalosis due to vomiting is a possible explanation for the high blood nitrogen. The mechanism of the rise in non-protein nitrogen would be similar to that of

TABLE IV  
Cases With Blood N.P.N. Above 50 Mg.\*

| Name  | N. P. N. | Urea  | Creatinine | Liver Pathology                                     | Kidney Pathology                                        | Associated Pathology  |
|-------|----------|-------|------------|-----------------------------------------------------|---------------------------------------------------------|-----------------------|
| U. E. | 94.8     | 120.5 | 3.3        | Central Necrosis.                                   | No pathology except bile nephrosis.                     |                       |
| A. N. | 50.1     | 53.0  | 1.92       | Acute yellow atrophy.                               | No pathology except bile nephrosis.                     |                       |
| S. G. | 150.0    | 229.5 | 4.92       | Central Necrosis (Chloroform).                      | No pathology except bile nephrosis.                     | Broncho-pneumonia.    |
| F. K. | 52       | 40.5  | 1.42       | Cirrhosis with early ac. yellow atrophy.            | Horseshoe Kidney—micro. negative except bile nephrosis. |                       |
| F. M. | 222      | 255.6 | 10.        | Cirrhosis with active hepatitis fatty infiltration. | Bile nephrosis chr. focal nephritis.                    | Chronic pancreatitis. |
| A. P. | 120      | 128.4 | 6.28       | Cirrhosis, fatty degeneration.                      | Bile nephrosis, chr. glom. nephritis.                   |                       |
| S. K. | 100      | 145.5 | 4.6        | Cloudy swelling of liver.                           | No pathology except bile nephrosis.                     |                       |

\*All figures in this table refer to mg. per 100 cc.

#### INSTANCES EXHIBITING HIGH NON-PROTEIN NITROGEN

The non-protein nitrogenous constituents of the blood displayed a remarkable and unlooked for behaviour, seven of the twenty-one cases had a blood nitrogen in excess of 50 mg. per 100 c.c. The current belief is that the blood urea is diminished in liver necrosis and insufficiency, since the liver is the sole site for urea formation. Mann (8) and his co-workers have noted that, in the hepatectomized dog, there was a progressive decrease of the urea in the urine and in a few hours scarcely any was present in the blood, urine or tissues. (If the dog's kidneys were removed at the time Mann removed the liver, he noted that the urea content of the blood was stationary; if the kidneys were removed before removal of the liver there was increase in the blood urea, and after hepatectomy this high level was maintained but not accentuated.)

Table IV summarizes the pathology encountered in seven cases of hepatic jaundice having a blood nitrogen over 50 mg.

Renal pathology was demonstrated in only two of the seven cases, one case showing focal nephritis and one chronic glomerulonephritis. In these two cases, there was enough obvious renal pathology to cause a nitrogen retention. In the remaining five cases, the only renal pathology present was bile nephrosis, i.e., pigmentation, and cloudy swelling of the tubular epithelium.

high intestinal obstruction where a depletion of chlorides by vomiting of hydrochloric acid causes the syndrome of high non-protein nitrogen, high carbon dioxide combining power and low blood chlorides. The blood chlorides were determined in one case (333 mg. per 100 c.c.) and the CO<sub>2</sub> combining power was not estimated. Vomiting was a prominent symptom in four of the seven cases with a high non-protein nitrogen.

The renal lesion accompanying liver necrosis undoubtedly explains some of these cases with a high blood non-protein nitrogen. Thus, Helwig and Orr (10) reported a case of injury to the liver with pulpification of the liver tissue and anuria progressing to uremia accompanied by high non-protein nitrogen terminally. Autopsy revealed a pulpified liver and a high grade nephrosis. Helwig and Schutz (11) reported five cases of long standing gall bladder disease, who, before operation, had normal blood and urinary findings, but who after operation developed this liver-kidney syndrome. With its appearance there were abdominal distention, fever, tachycardia, progressive oliguria, and albumin, casts and often blood in the urine. Nausea and vomiting occurred on the fifth to eighth post-operative day; there was bleeding from the mucous surfaces and the patients lapsed into a muttering delirium and finally coma. The blood nitrogen increased and the urinary nitrogen decreased. Autopsy revealed a cloudy swelling, fatty degeneration and, in

some instances, necrosis of the liver cells. The kidneys showed marked tubular damage. Jaundice was present in only two of their six cases. Experimentally, ligation of the hepatic artery of rabbits reproduced the laboratory picture of oliguria, albumin and casts in the urine and a rising non-protein nitrogen.

The authors suggest that a toxin may have been produced by the degeneration of the liver cells which poisoned the kidney parenchyma and caused progressive degeneration and not infrequently complete necrosis of the tubular epithelium of the kidney.

Only two of our seven cases showed definite nephritis; the remaining five showing only bile nephrosis, a lesion not ordinarily accompanied by a nitrogen retention. Another explanation and one which seems to us to be the most logical is that the degenerative products of liver necrosis and insufficiency may inhibit renal function without alteration of renal structure, i. e., we have here a functional renal insufficiency of such short duration that anatomical lesions are not yet definite.

Recapitulating, it would appear that while the rise in the non-protein nitrogen is not clear in all cases, the explanation, where no obvious kidney lesions are present, lies probably in the realm of insufficient renal function.

### SUMMARY

The etiology and symptoms of twenty-one cases of hepatic icterus are discussed.

Identical clinical symptoms, labelled "icterus gravis" can be caused by liver necrosis, cirrhosis without necrosis, cloudy swelling and fatty degeneration of the liver.

Icterus gravis may result from some known poison, unknown toxin or be a terminal event in a previously damaged liver.

Jaundice does not invariably accompany liver necrosis.

Multiple etiologic factors are often present in icterus gravis.

Infectious hepatitis where the source of the infection is not apparent may simulate icterus gravis.

Seven cases of hepatic icterus associated with blood non-protein nitrogen levels in excess of 50 mg. per 100 c.c. were observed. Only two of these cases had nephritis; the remaining five presented only bile nephrosis, a condition usually not associated with nitrogen retention. Several mechanisms are discussed to explain the dearth of renal findings in these cases, the most probable being that of impaired renal function, due to an acute lesion too short in duration to cause demonstrable structural alterations.

Nitrogen retention occurs frequently in terminal liver disease. It may be, but is not necessarily accompanied by gross renal damage.

### REFERENCES

1. Lepelme, George. Die Erkrankungen der Leber und Gallenwege; J. F. Lehmanns Verlag, Munich, 1930.
2. Kerr, W. J., and Rusk, G. Y.: Acute yellow atrophy associated with hyperthyroidism. *M. Clin. North America*, 6:445-459, Sept., 1922.
3. Barker, L. F.: Thyreo-intoxication with necrosis and atrophy of liver, damage to heart muscle and kidneys, and terminal bronchopneumonia. *M. Clin. North America*, 14:261-263, July, 1930.
4. Weaver, D. C., and Pemberton, J. de J.: Pathologic anatomy of liver in exophthalmic goitre. *Ann. Int. Med.*, 7:667-708, Dec., 1933.
5. Cave, H. W.: Dangers incident to cholecystectomy. *Ann. Surg.*, 81:371-378, Sept., 1926.
6. Heyd, C. G.: "Liver Deaths" in surgery of Gall Bladder. *J. A. M. A.*, 97:1817-1818, Dec. 19, 1931.
7. Elias, S.: Conservation of hepatic function in gall bladder operations; precautionary measures to prevent "liver deaths." *Ann. Surg.*, 98:348-353, Sept., 1933.
8. Mann, F. C.: The effects of complete and of partial removal of the liver. *Medicine*, 6:410-511, Dec., 1927.
9. Rubinowitch, I. M.: Biochemical findings in rare case of acute yellow atrophy of liver, with particular reference to origin of urea in body. *J. Biol. Chem.*, 83:333-335, Aug., 1929.
10. Helwig, F. C., and Orr, T. G.: Traumatic necrosis of liver with extensive retention of creatinine and high grade nephrosis. *Arch. Surg.*, 24:136-144, Jan., 1932.
11. Helwig, F. C., and Schutz, C. B.: Liver-kidney syndrome; clinical, pathologic and experimental studies. *S. G. O.*, 55:570-580, Nov., 1932.

## A Clinical Review of Giardiasis

### Twenty-two Cases Observed During Study of 572 Private Patients

By

G. S. de PAULA e SILVA, M.D.  
BELLO-HORIZONTE, BRAZIL

FOR years many authors have published regarding patients harboring giardia (lamblia) in the duodenum. The subject is still a matter of wide discussion and we are very far from a general agreement.

In this paper it will be shown what was observed in a group of patients that had in the bile, drained according to the world-known method of Lyon (1), abundant motile forms of this flagellate.

### INCIDENCE

Working in Bello-Horizonte, Brazil, in the tropical zone, in a series of 572 patients observed in private practice, from April, 1933, to February, 1935, I found this type of infestation only 22 times (cases Nos. 38, 43,

84, 126, 140, 197A, 283, 286, 292, 358, 372, 394, 409, 419, 439, 456, 514, 518, 533, 554, 557, and 566). There was, therefore, an incidence of only 3.8%. A case was not included that presented diarrhea and giardia in the stools; the drainage, made after the treatment of the diarrhea, showed no parasite in the duodenal contents. Of these 22 patients 15 were males and 7 females. The age varied between 18 to 61 years.

This study concerned only private patient material; neither the cases seen in the ward nor these examined in other services were included. Recently, Prof. Alfredo Balena (2) has published a series of papers concerning cases observed in his ward services, where I am an



assistant. It has been his observation, and also mine, that giardiasis occurs with much greater frequency among the poor than among the well-to-do, because of greater contamination of water supply, vegetable and fruits.

### DIAGNOSIS

In all my patients the diagnosis was made after drainage of the gall tract, as referred to above. In this series 112 drainages were performed for diagnostic and control purposes on different occasions. In every case several samples of the draining bile were collected in large centrifuge tubes and centrifuged for 10 minutes (3,500 revolutions a minute). With the material thus collected in the bottom of the tubes several slides were prepared promptly and carefully examined, while warm, by the microscope.

In only one stool examination, in this series, cysts of giardia were found 12 times (54%); even with repeated examinations some patients gave persistently negative results (one with 15 repeated examinations).

### SYMPTOMS

So frequently the coincidence of symptoms was observed in the bearers of these flagellates, symptoms that decreased and vanished with the elimination of the parasites, that a relation of cause and effect had to be considered. It is never possible to assume that what the patient complains of actually represents symptoms solely due to the infestation he harbors. It is necessary to seek other correlated factors and to estimate to what extent the giardia can be responsible for the clinical picture. In this series 3 cases showed symptoms that later could not be explained as being caused by the infestation: two with digestive complaints, and one patient with vertigo and diarrhea in whom the treatment failed and, with it, the therapeutic test.

The time of onset of the symptoms varied in this series between 5 months and 49 years. The symptoms presented by the patients can be arranged in 3 groups:

A. Symptoms attributed to the infestation of the duodenum and gall tract.

B. Symptoms attributed to a wider infestation of the intestines other than the duodenum.

C. Systemic symptoms.

#### A-I

A. The symptoms attributed to the infestation of the duodenum and gall tract consisted mainly of painful manifestations, frequently associated with dyspeptic symptoms, as follows: 1. Severe pain, like biliary colic—seven patients complained of severe pain in the epigastrium and right hypochondrium, radiating to the back (3 cases) and to the right shoulder (1 case), with all the features of colics due to stones; one patient showed evidence of co-existing stones. Unhappily, the existence of stone in this case and the non-existence in the others could not be proved since their gall-bladders were not surgically removed to examine the contents.

Well performed radiologic examinations, only possible in 3 patients, were not of help: one showed good visualization with a normal gall-bladder shadow, and in the others there was no visualization of the gall-bladder by the contrast dye.

Only one patient presented in the sediment of the bile, cholesterol crystals (abundant) and calcium bilirubinate. This case continued to present colics after the removal of the parasites whereas 4 improved in which the treatment also brought disappearance of

the giardia. This coincidence of being the only patient that showed cholesterol crystals and calcium bilirubinate in the sediment of the bile and the only one of the group in which the long treatment directed against the giardia did succeed without disappearance of the symptoms, suggests the possibility of lithiasis; in this case the X-ray examination revealed no visualization of the gall-bladder.

If a patient complains of attacks of colics like these which occur with the finding of abundant giardia in the biles, and if these colics then disappear after the parasites are eliminated then the most logical standpoint is to infer this may be cause and effect. Of the seven patients two are still under treatment at this time.

Only further observation of such patients will show that this diagnostic inference is correct in as much as the history of these patients indicates that, in the large majority, there is a long interval between the painful crises. Therefore, there must be a long follow-up period of observation. For instance, female patient 394, until 2 years before the examination had had annual crises and, since then, had entered a quiet period; also case 557, a male, had had crises in 1912, 1920 and 1929; and female patient 439 had had, 6 years ago, a period of 12 days with colics and none since. Two other patients suffered crises recently and no conclusion, therefore, can be drawn. Only one patient, a male, had severe colics within an interval of 4 months, after driving through bad roads; this man was benefited by the treatment. No patient developed jaundice during the colics; only the female patient 394 observed herself moderate scleral jaundice.

With this frequently long interval between the colics we are prone to judge the results of treatment based upon the disappearance of collateral symptoms that annoyed the patient. These were mainly dyspeptic in nature. After meals they were apt to feel a sense of weight in the epigastrium (2 cases), fullness (4 cases), distress (3 cases); in two instances nausea and vomitus with relief of symptoms (in one the vomitus was induced); pyrosis and eructations (2 cases).

The radiologic examination of stomach and duodenum, performed according to Berg's technique in 5 of these 7 patients, gave normal results in 4 instances; in one—patient 292—was found a duodenal ulcer.

The physical examination in these cases was possible to be made during the colics in only two instances: the patients presented pronounced soreness in the upper abdomen and resistance of the parietes. Between the crises as made in the other 4 cases (not including the one suspicious of lithiasis) the examination revealed tenderness over the right upper quadrant in all cases and over the epigastric region in 3 cases; there was no evidence of enlargement of the liver. As advised by Crohn (3), we performed the Libman test (pain on pressure over the styloid process) to detect the sensitiveness to pain of these cases. Of these 6 patients, 4 had +++ and 1 had ++; one not performed. So, there is marked predominance of the hypersensitive type.

II. Upper abdominal pains, without the character of colics (6 patients) or during the interval of the colics (3 cases) were also found. The following distributions could be made:

a. Pain soon after meals, in two patients, localized in the epigastrium (radiating to the back in one

of them), accompanied by nausea, sense of fullness, pyrosis, vomiting with relief. Careful X-ray examination showed nothing abnormal in one of the cases in the stomach and duodenum. Physical examination revealed in both cases the epigastric and the gall-bladder regions painful on pressure. The Libman test, in one case + + +. Both are under treatment.

b. Late pains, in two cases, in these patients the pain appeared from 2 to 3 hours after meals, accompanied by distress, a sense of weight and fullness in the epigastrium. There was no relief with food. Sometimes the pain was continuous or appeared during the night. The X-ray revealed in one case a duodenal ulcer, and nothing abnormal in the stomach and duodenum of the other. The physical examination showed in both, the right upper quadrant painful on pressure; in one the epigastric region was also painful; there was no evidence of enlargement of the liver.

c. Irregular or continuous pains in the upper abdomen were found in 5 patients. In 3 instances there was radiation to the back. Two felt the pains also during the night. Only one had no digestive complaints. Of the other 4, 3 had sense of weight in the epigastrium after meals; 3 had a sense of fullness; one had eructations; one had pyrosis; and one vomited.

The physical examination during the pain crises was possible only in two patients. One had more severe pain in the left hypochondrium, radiating to the back; the other seen some hours after the onset of the pain, still had upper abdominal tenderness on pressure in the epigastric region and two, also, in the upper abdominal tenderness. Of the remaining 3 patients, all presented tenderness on pressure in the epigastric region and two, also, in the upper right quadrant. Of these patients but one presented evidence of slight enlargement of the liver (during the painful crisis). The radiologic examination of the digestive tract revealed in this group, intermittent duodenal stasis and appendicitis, one instance; "duodenitis descendens," 1 instance; organic duodenal stasis, 1 case; the fourth was normal.

III. Dyspeptic complaints, not associated with pain were presented by only one patient. These complaints (certain sense of weight after meals, fullness and distress) were very infrequent and slight; physical examination gave normal results. As shown above, the dyspeptic complaints were always associated with painful manifestations. This fact is to be emphasized.

#### B

Symptoms attributed to a wider infestation of the intestines were neither constant nor uniform. Of this series of 22 patients, 9 had regular bowel movements; 4 had alternation of constipation and diarrhea; 6 had attacks of diarrhea; 2 had moderate constipation.

During diarrhea attacks 3 had tenesmas. Frequency of evacuations was, during these attacks, variable (up to 20 times a day); the feces were watery or mushy, without blood (only once a patient noted some red streaking); the stool examination revealed some mucus in 6 cases.

The physical examination revealed a certain degree of spasticity of descending colon and sigmoid in 7 patients.

#### C

Systemic symptoms are rather polymorphous. Five patients had loss of weight; 3 complained of insomnia; 6 had nervousness and irritability; 5 had

headaches during the morning or associated with digestive troubles; 3 had hemicranial attacks coincident with digestive troubles.

Special attention must be directed to two cases in which the most striking feature was fever. The fever was irregular, appearing either during the morning or during the afternoon, oscillating up to 106° Fahrenheit; it lasted a variable number of days and disappeared without following any particular type. In one patient the fever lasted one month without interruption. Besides the fever, the patient presented pronounced weakness, uneasiness, vomiting, great loss of weight and diarrhea. A maximum of 20 movements a day was reached; stools were watery, with some mucus, but without blood. This puzzling picture challenged the most refined judgment, and plenty of tests were performed until the finding of the flagellates and proper treatment cleared the situation. One of the patients was seen during an afebrile period, but numerous giardias were found in his watery stools during the febrile period. The other case received, without benefit, quinine and arsenic, for the suspicion of malaria had arisen, although the examination of the blood for plasmodia was negative. There was no jaundice in either case. Reviewing the records of the other cases, in 4 instances it was found the incidence of fever not quite surely explained.

Of the series only a female patient presented jaundice, but not attributable to giardia. She was the third member of a family of two brothers I examined who had hemolytic jaundice. In her case all the features suggested a hemolytic origin of the jaundice.

Summarizing, the complaints that obliged the patient to consult the physician were: Painful manifestations in the upper abdomen, frequently associated with digestive troubles, in 13 cases; fever and diarrhea, 2 cases; diarrhea, 1; loss of weight, 2; slight and inconstant digestive troubles, 1. Three cases in which giardia could not be considered as being the cause were excluded (two with digestive symptoms and one with vertigo and diarrhea).

#### TREATMENT

While some authors either do not treat or give but slight treatment for giardiasis, considering it of no pathogenic importance, I insist upon using medicines, and in repeated intensive courses. After many trials and failures, I adopted the combination of neosalvarsan by vein, after a good drainage of the gall tract, and stovarsol and yatren 105 by mouth, intensively.

Neosalvarsan was used to combat giardiasis in 1917 by Yakimoff (4) in white mice. Hollander (5), in 1923, used it in 3 patients. Lyon and Sevalen (6) used drainage of the gall-tract and intraduodenal injection of neosalvarsan and other medicines.

Either etovarsol or yatren were used by Castex and Greenway, but in smaller doses than those used by me. Also attention should be directed to certain publications by Smithies (8) who first called attention to giardiasis of the gall-bladder and first suggested the use of arsenic and mercury (calomel) in therapy.

During the first period of the treatment (20 to 25 days,) when biliary drainage are performed at intervals of 5 days, followed by intravenous injections of neosalvarsan, I use stovarsol and yatren without the intervals that are advised by the authors. The biliary drainages, well done, help to detoxify the patients.

During the second period, when the drainages are done at longer intervals, for control purposes, the doses of stovarsol and yatren are much smaller and, as a rule, well tolerated by the patients.

Before beginning the treatment and during its administration it is necessary to take some precautions. Beside the accurate clinical general examination to detect some sign of intoxication (erythema, skin eruptions, suborbital edema etc.) some laboratory tests are indicated. In the blood, icterus index or Van den Bergh. In the urine, careful examination of the sediment of a fresh specimen for albumin, blood, urobilinogen, biliary salts and biliary pigments. At least these precautions have to be taken before each injection of neosalvarsan and, later, at monthly intervals, during the treatment by mouth.

#### TECHNIQUE OF THE TREATMENT

**First Period (20 to 25 days):** During the morning the duodenal tube is passed and, when in place, 30 c.c. of a 30% mg.  $\text{SO}_4$  solution are slowly introduced. The bile is allowed to drain, and instillations of 20 c.c. of the mg.  $\text{SO}_4$  solution are given in repeated doses, until no more concentrated bile is obtained. After this good drainage the tube is removed. An intravenous injection of 0.30 to 0.45 gm. of neosalvarsan is given. Two tablets of 0.25 gr. of stovarsol are diluted in half-a-glass of water and taken by the patient, who is sent home, being advised to have a certain rest and "light" diet. In this same day at 3 P.M. and before retiring he takes 3 pills of 0.25 gm. of yatren, each time.

This whole procedure is repeated every 5 days, although the flagellates usually disappear after the second or third drainage. It is advisable to administer 4 to 5 injections (always preceded by the drainage, well done) of neosalvarsan (0.45 gm.). This is important.

Between these seances of drainage—neosalvarsan the patient takes, daily: before breakfast 2 tablets of stovarsol; at 12 M. three pills of yatren; at 5 P. M. one tablet of stovarsol; being retiring, 3 pills of yatren. The appearance of diarrhea is not uncommon due to the use of yatren.

**Second Period:** After the last drainage—neo-

salvarsan seance the patient begins to decrease the doses of stovarsol and yatren. During the following 5 days he only uses 2 tablets of stovarsol on rising and 3 pills of yatren on retiring. After these five days he then uses 1 tablet of stovarsol while fasting and 2 pills of yatren before going to bed. The use of stovarsol and yatren in the last manner is carried on for 6 months. Control examinations of duodenal contents are made after 1, 2 6 and 12 months, at least.

#### RESULTS

It is too early to speak surely about the end-results of the treatment. The longest period of control we have is now only 7 months. But the patients, in the majority, feel well, the annoying symptoms disappear, and only upon repeated requests will they return for control examinations. Thus they appear to be clinically cured.

Of this series of 22 patients, 16 had followed the treatment in such a way as to authorize us to speak about results.

One patient continues to harbor the parasites; another also continues to be infested (in this case the initial dose of neosalvarsan was 0.15 gm., too little), these two patients did not use yatren.

In 14 patients it was possible to get the bile free from the parasites over a period now (February 1935) of seven months. Further examinations will show the possibilities of relapse, if such occurs.

**Accidents:** As a rule all this intensive treatment runs without accident. The beneficial effects of the well done drainages is to be recalled.

One patient developed jaundice during the treatment; the outline of the treatment was made by me but executed in a distant town by a local doctor. I had not sufficient data to judge this accident. It may have been an arsenical jaundice.

The subject of giardiasis is still open to discussion until further well conducted studies bring a better understanding of the clinical picture and the necessary treatment.

**NOTE:** I wish to express my thanks to Dr. B. B. Vincent Lyon, of Philadelphia, for his criticism and advice in the writing and arrangement of this paper.

#### REFERENCES

1. Lyon, B. B. Vincent: Non-surgical drainage of the Gall Tract. Lea & Febiger, 1923. Chap. XVI, XVII, and XXII.
2. Balenn, Alfredo: Giardiose biliar. *Brasil Medico*, 1935, Jnn. 19, p. 47.
3. Crohn, B. B.: Affections of the Stomach, Saunders, 1927, p. 272.
4. Yakimoff, quoted by Hollander.
5. Hollander, Edward: Giardiasis infection, *Arch. Int. Med.*, 1923, 32, 522.
6. Lyon, B. B. Vincent, and Swalm, William A.: Giardiasis: Its frequency, recognition, treatment and certain clinical features. *Am. Jour. Med. Sc.*, 1925, 170, 348.
7. Castex W., and Greenway, Daniel, quoted by Lyon (6).
8. Smithies, Frank: Biliary tract protozoosis. *Trans. Chicago Path. Soc.*, 12:331-333, June 1, 1927.

Parasitosis of bile passages and gall bladder. *Am. Jour. Med. Sc.*, 176: 225-253, Aug. 1928.

## A Consideration of the Patient with Gastrointestinal Complaints but Who is Without Evidences of Organic Pathology\*

By

G. ALEXANDER YOUNG, M.D.

and

RICHARD H. YOUNG, M.D.

OMAHA, NEBRASKA

**T**HE intake of food, the processes of digestion and elimination play such important rôles in our existence as individuals that any disorder of these functions

\*From the Department of Neurology and Psychiatry, Univ. of Nebraska School of Medicine. Submitted, March 12, 1935.

assumes considerable importance. The complaints produced by dysfunction of the gastrointestinal tract are among the most common symptoms for which a patient seeks relief. So frequently are gastrointestinal complaints encountered, that it seems worth while to re-

formulate a plan for study of these cases and to consider particularly those cases who have complaints without evidence of organic disease.

In any medical case, the physician starts with certain facts, *i.e.*, the complaints as given by the patient. A scientific approach next leads us to consider the conditions under which the complaint developed, then the course, and finally the picture at the time of examination. These facts are further embellished by the data that are obtained from a past and family history. When the facts are assembled conclusions are drawn as to whether this is a case of a local disturbance or whether the symptoms are secondary to a more sweeping systemic disorder.

The above is a usual procedure which paves the way to a diagnosis. The final interpretation usually is in terms of some organ pathology or disease process which affects the function of the gastrointestinal system. The differential diagnosis in cases of abdominal distress is too long to consider here but our whole training as physicians (which has become more and more scientific) has developed the questionable habit of expecting to find something organically wrong in all of these patients. This attitude or habit of thought has, in turn, led to the subjection of countless patients to abdominal operative procedures which besides being unwarranted have been entirely devoid of any benefit, and at times harmful. These patients have been operated upon in good faith with the hope of finding the organic disease that was not discernible by the usual diagnostic methods.

Medicine tends to reduce disease to organ pathology with the interpretation of distress in relation to nearby referable somatic or visceral structures. We study "part" or organ functions but learn little about how they serve the individual in their reciprocal relations as integrated parts of the "he" or "she" we administer to as patients. A symptom such as vomiting or diarrhea is considered as a "non-mental" fact, a symptom produced by the disorder of an organ or system of organs. However, our knowledge of individuals, a knowledge usually not obtained in a medical amphitheatre, tells us that an anxious, fearful individual may have a diarrhea and that an individual who has experienced a sharp reaction of disgust may vomit. These facts we might call "mental" facts, or better "personality reactions", the reactions of the personality of an emotional nature to a situation of strain. It is with such facts that the physician must interest himself. Our present day mores, totems and taboos, the economic depression, the competition in work, and attempts to make a satisfactory marital adjustment are productive of situations of stress and strain and at times color our lives with rather unpleasant personality reactions. About one person in every seventy reacts in such a way to these strains that a period of care in a psychiatric institution is necessary at some time in his life.

As individuals we are so integrated that, in situations of strain, our bodies protest. Cannon and other physiologists have shown the sweeping physiological changes that accompany emotional states. Alvarez at the Mayo Clinic has done gastroenterology a great service by repeatedly emphasizing the fact that the emotional states affect the gastrointestinal tract and are productive of symptoms.

The question arises as to how the physician can utilize the fact that personality disorders play a role

in the production of gastrointestinal complaints. In the first place, there must be the realization that we are dealing with an individual who has certain complaints. These complaints must not be classified on the "either—or" principle, due either to organic or to functional cause. A patient may be anxious, tense, fearful of the future with an ulcer in his duodenum. It is important to consider all the facts both organic and functional.

In order to evaluate the rôle that the personality functions play it is necessary to quiz each case as to the personality reactions. This can be done simply without resorting to a formal mental status. Alvarez has found it very useful to ask his patients with gastrointestinal complaints if they have any trouble reading. This simple question usually reveals any thinking disorder. Thinking disorders are present in the schizophrenic disorders, the depressions and with many of the psychoneurotic difficulties. Lewellys Barker and others inquire as to the patient's mood or spirits. This usually allows some evaluation of the affective state; whether the patient is depressed, anxious, fearful or tense. Simple questions about worries or concerns, whether the patient feels the world treats him well and about sleep may be very informative. These very few interrogations may allow a formulation of the personality reaction and a classification of the reaction type which is responsible for a part or all of the gastrointestinal distress. Some of the more usual reaction types which furnish the basis for gastrointestinal complaints may be mentioned.

#### ANXIETY AND TENSION STATES

The anxious individual usually appears tense and concerned. He may be tremulous with perspiring hands. While the majority of the body complaints associated with this reaction type are above the diaphragm there may be certain symptoms referable to the gastrointestinal tract. A very frequent complaint is a tightness or constriction in the throat (*globus*) which at times is said to interfere with swallowing. Occasionally there are vague abdominal complaints of "gas" and epigastric discomfort. This may be in part due to an increased gastric acidity that at times is associated with an anxiety state. Diarrhea is another occasional accompaniment of anxiety and tension. Medical students each year develop gastro-intestinal complaints and even flares-up of ulcer under the stress of the examination period.

The production of gastrointestinal complaints in a situation of anxiety and tension is well illustrated by the following briefly reported instance:

L. B. A 25 yr. old farmer complained of gas and digestive distress. About a year ago he developed a vague mid-abdominal distress for which no adequate cause could be determined. This failed to yield to usual forms of treatment and during the winter an appendectomy was done with the thought that this organ might be at fault. The distress continued and in July of this year he sought out another physician who questioned him as to masturbation. The man admitted it and was then told that his prostate was about twice normal size, that he probably would have to experience a serious operation in years to come, that he should give up his plans for marriage and stop masturbating. The patient became rapidly worse and sank into a depression which allowed him little sleep, with more body complaints including a fullness in the rectum, thought of a self-condemnatory nature and a serious consideration of suicide. In going into the history we find that this man's initial gastrointestinal complaints came on in a situation of anxiety and tension. A year ago he was anx-

ious to marry a young woman in his neighborhood. The marriage had not been consummated because of financial difficulties and because of his own vague fears about his potency as a result of masturbation. He was haunted by some of the folklore which he had heard as a youth to the effect that he wasted a "seed" each time he masturbated and he was fearful that the supply had been exhausted. This anxiety plus the increased sex tension which developed as the result of the frustraneous sex excitement of the engagement undoubtedly were the main factors in the production of his complaints. In this situation appendectomy could offer little help. His interview in July only served to confirm his worst fears and the man slid into a depression which complicated his treatment immeasurably.

#### INVALID STATES

A second reaction type in which one finds gastrointestinal complaints is the invalid state. This is the so-called hypochondriasis of a simple type, invalidism without any depression or evidence of a more sweeping disorder. The invalid is one who is greatly preoccupied with his or her body complaints. The complaints are almost delusional in type and attributed to effects of exaggerated disorders of the gastrointestinal tract. The patient is not infrequently the victim of infection with an organic diagnosis, is bound down by "adhesions" to habits of invalidism, is very inactive, excessively particular about the diet, imposes upon himself long periods of bed rest and enjoys the satisfying attention of friends, neighbors and family.

#### DEPRESSIVE STATES

A third personality reaction type productive of gastrointestinal symptoms is the depressive state. The person depressed is slowed down, feels "low," "sad," "unhappy," or "blue." There are usually the physiological accompaniments of constipation, poor sleep, appetite and weight loss. Henry and others have shown the physiological changes in the gastrointestinal tracts of depressed patients that cause the abdominal distress that is frequently present. It is surprising how frequently the depressed patient complains of poor appetite, constipation and "gas on the stomach." Occasionally cases are seen where the gastrointestinal complaints are present before the mood disturbance is noticeable. Such cases are spoken of as having gastrointestinal "equivalents" of depression. The abdominal distress is a visceral expression of the mood disorder. A case under observation this past year illustrates this point.

H. R. is a 47 year old business executive who a year ago began to complain of digestive distress of the so-called ulcer type; the distress came on several hours after meals and was relieved by eating or soda. He did not respond to the usual Sippy *regime* and some months later because of poor sleep and weight loss he sought psychiatric consultation. When examined he was found to be tense, anxious, depressed and fearful that he was going through a depression such as he had experienced fifteen years before. He became more depressed and as the mood disturbance came to the foreground the digestive distress disappeared. The gastric analysis showed a rather marked hyperacidity at the onset. A gastro-intestinal Roentgen series showed no evidence of an active ulcer and a cholecystogram was normal. The depressed period lasted a matter of six months and gradually disappeared. However, after the mood became normal, the gastrointestinal complaints reappeared. After a difficult period these in turn faded. Here we find digestive distress ushering in the depression as an "equivalent" and reappearing at the end of the illness to disappear with complete recovery.

Other personality reaction types may feature gastrointestinal complaints. One should mention the schizophrenic reactions, those queer, twisted types, and where there are complaints of a *bizarre* nature or those which have an odd ring, e.g., "feel as though there is something firey that runs from one side of my abdomen to the other and then shoots out my rectum," one should be suspicious of an underlying schizophrenia. The same would be true where one encounters an empty, flat, abdomen with hypochondriacal harping on certain digestive complaints.

#### TREATMENT

Physicians everywhere have a tendency to rationalize their own lack of interest in the so-called "functional" cases by the thought that little can be done for them. Too often the symptoms are passed off as "imagination" or there is a careless reduction of the difficulty to some organ pathology even though none is found. The majority of these cases can be handled by the general practitioner if he will but interest himself in their care.

Treatment cannot be based solely upon management of the alimentary tract or treatment directed to any given organ. It is necessary to treat the individual and the personality reaction. In doing this perhaps the best help is to provide the patient with an opportunity to talk. In our present day handling of the behavior disorders there is too often a tendency to disturb the patient by an aggressive search for sexual difficulties. This may be harmful particularly in the major mental illnesses and cause the patient to erect a defensive wall to further questioning. This tendency has developed as the result of attempt to obtain rapidly a finished dynamic picture which satisfies the etiological needs of the physician but which is of no consolation to the patient.

Once *rapport* has been established and examination has shown there is no evidence of a disease process then the diagnosis should be stated in unequivocal form. The interpretation of the illness must of necessity depend upon the intellectual assets of the patient. His difficulty should be explained to him as a personality reaction to a situational strain causing emotional features and nervousness that so affects the body physiology as to cause symptoms of distress. The digestive distress may be termed the body's protest to a situation of strain. Reassurance should be given and if the dynamic factors are forthcoming, a common-sense discussion of these factors will be of benefit. The simplest methods of treatment are sometimes the best and simple types of regulation with removal of the patient from the situation of strain may afford great help.

In the case of the invalid one should attempt to break up the "adhesions" which bind the patient down. The patient should be given a regime of activity that fills the day. This requires careful thought and imagination on the part of the physician.

Where the symptoms appear in a depressive setting the problem is more difficult. A depressive reaction always is charged with the danger of self-destruction and every depressed patient should be considered a suicidal risk. For this reason such cases are best cared for in specially equipped hospitals. Medical treatment in the form of broken doses of barbitol or its derivatives is indicated. Mineral oil usually corrects the constipation. A high caloric diet should be



forced when there is weight loss. Hydrotherapy in the form of tubs or packs is indicated to relieve tension. A probing into psychogenic factors had best be avoided early in the treatment for fear of stirring up material that cannot be digested in a depressed state.

In cases where the gastrointestinal complaints are features of a schizophrenic reaction type the patient will need care in a psychiatric hospital.

Medicine should be used sparingly and when given the reason clearly stated. Bromides must be used carefully because of the danger of a bromide intoxication with delirium. This is particularly true in cases where there is any cerebral vascular pathology because bromides have a depressive effect upon the vascular system and these individuals show signs of intoxication with rather small amounts of bromides.

## SUMMARY

In summary, it is urged that in consideration of any case with digestive complaints the attempt be not made to reduce the condition to an "either—or" basis. Cases are not either organic or functional. In any diagnostic problem one must consider all the facts, non-mental and mental; facts dealing with organ functions and personality functions. To do this one must make inquiry as to the mood, as to whether there is thinking difficulty and as to the thought trend. If there is some personality difficulty it can best be reached by studying the conditions and situations in which it developed. The care of the milder forms of disorders can be best handled by an acute interest in the difficulty, by providing the patient opportunity for discussion and by the use of common sense and a certain imagination in management.

## Non-tuberculous Mesenteric Lymphadenitis in Childhood\*

By

LOUIS H. SEGAR, M.D.

and

B. D. ROSENAK, M.D.

INDIANAPOLIS, INDIANA

**M**OST physicians have seen children who complain of abdominal pain and other gastro-intestinal symptoms which are due apparently to intra-abdominal disease and yet defy satisfactory diagnosis. These cases may suggest the presence of any of several disorders, but most often they simulate appendicitis. We believe these gastro-intestinal disturbances to be more often associated with mesenteric lymphadenitis than is commonly supposed.

Tuberculosis of the mesenteric lymph nodes, known for many years as *tuberculosis mesenterica*, is a commonly acknowledged cause of acute abdominal symptoms. Less has been written of non-tuberculous mesenteric lymphadenitis. This condition was known to physicians of the past as "strumous abdomen" and was given credit for its ability to mimic most intra-abdominal diseases. However, Braithwaite and others deny that non-tuberculous mesenteric lymphadenitis exists as a cause of abdominal symptoms.

Heusser has reported 40 cases of mesenteric lymphadenitis in which tuberculosis was carefully ruled out by negative guinea pig inoculations, negative cultures and negative anti-formin examinations. Speese has seen 57 cases in which the glands removed at operation were non-tuberculous. In 281 routine autopsies at the James Whitecomb Riley Hospital for Children there were 32 cases or 11% which showed non-tuberculous hyperplasia of the mesenteric lymph nodes. In this group there was a high incidence of previously existing entero-colitis. Irwin found enlarged mesenteric lymph nodes in 53 of 375 patients operated on for various abdominal conditions. Clute states that only 18—

22%—of the mesenteric nodes examined from the autopsy material at the Lahey clinic were tuberculous.

Non-tuberculous mesenteric lymphadenitis is seen most often in childhood. The ages in the group here reported were from 2 months to 12 years. Of Heusser's 40 cases, 29 were in children under 15. More than 50% of Speese's patients were under 12. Alvarez has, however, seen several cases in adults.

## PATHOLOGIC ANATOMY

The lymph nodes of the terminal ileum, cecum and appendix lie along the mesenteric attachment of the viscera and drain into the regional nodes between the leaves of the mesentery. These are the nodes most frequently involved in both tuberculous and non-tuberculous mesenteric adenitis. The direction of lymph flow is upward into the *cysterna chyli*. These glands constitute a part of the lymphatic system of the bowel which consists of the lacteals of the villi, Peyer's patches and the lymph vessels which drain into the mesenteric nodes. A striking analogy between the gross relationship of the units of the lymphatic system of the intestine and mesentery to those of the pharynx has been observed by Wilensky and Hahn. Alvarez quotes Adami as showing that bacteria and other material can be transmitted through the wall of the intestine by this lymphatic system in the absence of any lesion of the mucous membrane. Short and Speese have also pointed out that the normal bowel wall is permeable to bacteria. They state that the function of the mesenteric nodes is to deter bacteria and other foreign material which come from the intestines in the afferent lymph vessels. As in the cervical region, these nodes will remain normal as

\*From the Indiana University School of Medicine and Hospitals, Indianapolis.  
Submitted, March 16, 1935.



long as they are not overburdened with infectious material.

For many years physicians have regarded infections of the mesenteric lymph nodes as always being of tuberculous origin. It has been the general belief that this disease was due to bovine tubercle bacilli which gained entry to the alimentary tract in contaminated milk or food, or to human tubercle bacilli swallowed in the sputum from pulmonary lesions. Braithwaite maintains that all mesenteric lymphadenitis is tuberculous. He explains the simple inflammatory changes which are frequently encountered as being due to very early tuberculosis. Speese quotes Symmers as saying that the simple hyperplastic changes are due to the toxins of the tubercle bacilli. There is no doubt that tuberculous mesenteric lymphadenitis exists, and that the mode of infection might well be as described. But glands which are readily susceptible to this type of infection could hardly escape occasional infection by other pathogens which are even more abundant in the gastro-intestinal tract than the tubercle bacillus. The frequent association of abdominal symptoms in children having upper respiratory tract infections suggests strongly that the source of infectious material is the swallowed secretions from the nose and throat. Histologic examinations of large numbers of glands removed at operation consistently have shown simple hyperplastic changes with no evidence of caseation or tubercle formation. Bacteriologic studies likewise have been negative for acid fast bacilli in most cases. However, bacteriologic examinations in definitely non-tuberculous glands have not been very illuminating. In most instances no organisms have been recovered. Brown has mentioned cases in which streptococci have been found and he advises against the removal of glands for examination in these cases because of the danger of producing a peritonitis.

The favorable therapeutic results in many mesenteric adenopathies by laparotomy and general medical after care argue emphatically that the glandular involvement was not due to tuberculosis. Another consistent observation in these cases is the concomitant absence of a pulmonary tuberculosis; although Carson maintains that mesenteric lymphadenitis may constitute an independent focus of tuberculosis in the body. The undoubted occurrence of inflammatory processes involving mesenteric lymph nodes in very young children who have no history of tuberculous contacts and having negative intra-cutaneous tuberculin tests is conclusive evidence that infection of the mesenteric nodes is not always tuberculous.

The most frequent site of hyperplasia of the mesenteric glands is at the ileo-cecal angle. The reasons advanced by Clute, Speese, McFadden and others for this localization of the infection is that there is a greater concentration of bacteria in the bowel contents at this point and that the fecal flow is at low ebb. Others have speculated as to the part that the appendix might play in making this the site of predilection. Wilensky and Hahn regard the appendix as insignificant in the etiology of non-tuberculous mesenteric lymphadenitis. The majority of the cases reported in the literature had no significant pathologic changes in the appendix. Of the cases reported in this paper only one showed any inflammation in the appendix and that was an old inactive lesion. Most surgeons of experience have confirmed this observation. Nevertheless, Higgins quotes reports of 4 cases of suppuration of

the mesenteric lymph glands secondary to appendicitis, and Lamson has seen a case of acute mesenteric adenitis complicating an acute appendicitis. It is probably safe to conclude that mesenteric lymphadenitis does not often complicate appendicitis, and that this organ has nothing to do with the usual site of mesenteric lymphadenitis in the ileo-cecal region. Turberville has seen 2 cases of suppurative lymphadenitis in the mesentery of the left side of the abdomen. In the group of cases seen personally the glandular involvement was widespread throughout the abdomen in all of the younger children and was definitely localized in the right iliac fossa in the older ones.

The exceeding rarity of inflammation of the mesenteric lymph nodes in appendicitis has been pointed out. The occurrence of this type of lymphadenopathy in the absence of demonstrable lesions in the wall of the intestine itself is seen in this series of cases and has also been noted frequently by other writers. There remains for discussion the relationship of hypertrophy of the mesenteric lymph nodes to diseases involving the small intestine. Sporadic reports of cases of hypertrophic enteritis of the small intestine of a non-tuberculous nature dot the literature for many years. In 1932 Crohn and his associates reported a group of cases in which the pathological and clinical unity of a certain type of non-specific inflammation of the small intestine was clearly demonstrated. This disease has been termed "regional ileitis". In this group there was a constant thickening of the mesentery of the ileum and a simple inflammatory hypertrophy of the ileo-cecal lymph nodes. Most of the cases which we are reporting had no evidence of ileitis at operation or at autopsy. The last case cited falls into the group in which a definite inflammation and thickening of the terminal ileum was found. This case must be regarded as one of "regional ileitis" with secondary lymphadenitis leading to suppuration and mesenteric thrombosis. Since the description of this disease the diagnosis is being made with increasing frequency due to the greater care that surgeons are taking in exploration of the small intestine.

A. Rendle Short has specified that a normal mesenteric lymph node should be soft, discreet and no larger than a pea. It is impossible to make this description fit all normal mesenteric nodes. They may be considerably larger than Short specified and yet show no gross or microscopic pathologic anomalies. The gross pathologic abnormalities that may be encountered vary greatly. The glands may be markedly enlarged and reddened and yet be discrete. Such glands are usually the seat of an acute non-tuberculous infection; probably in most instances due to one or more of the pyogenic cocci. Others, of a more chronic type, are firm and matted together. These glands do not show caseation or tubercle formation. Frank suppuration of the nodes though rare has been reported by Turberville and by Higgins and was seen in one case of the present group. Calcification is regarded by Wilensky and Hahn as the terminal stage of all mesenteric adenitis whether tuberculous or not.

#### CLINICAL MANIFESTATIONS

*Pain* is the most constant and characteristic symptom of mesenteric lymphadenitis. Leonard Freeman in 1923 stressed the surgical significance of the condition and emphasized that abdominal colics were the most important and distinguishing feature of

the syndrome. He mentions that violent spasms of the bowel may be seen upon handling them during operations, and considers that the adenitis produces an irritability of the mesenteric nerves. Kiss, in a study of the relationship between nerve plexuses and lymph nodes of the abdomen, found that the mesenteric nodes follow the course of the superior and inferior mesenteric arteries and are found close to and often among the nerve fibers. He states that because of this anatomic association inflammation of these nodes may cause pain as well as functional disorders of the associated viscera. In addition to pain produced by intestinal colics the mesentery itself is able to cause abdominal pain. It is easily demonstrated that the abdominal viscera may under ordinary conditions be very roughly handled without producing pain, whereas the least pull or stretch of the mesentery is extremely painful. Thus, an infant with an intussusception is comfortable with a swollen engorged loop of bowel until a peristaltic wave attempts to pass and produces a strain on the mesentery. The mode of production of pain in mesenteric adenitis is by irritation of the Paeinian bodies which are the sensory nerve endings in the mesentery.

### CASE REPORTS

*Case 1.*—The first patient to be reported is a case in point. A boy 7 years old was brought for examination with the following history: Since infancy he had had many recurrent gastro-intestinal upsets with more or less abdominal discomfort of an indefinite sort, with vomiting and moderate rise of temperature. He had been a difficult feeding problem, had gained poorly and had had abdominal colic. He never had anything, however, that could be construed to be an acute enterocolitis. Of late his attacks had changed in character, and the father described them as follows: "Two or three times a week after taking a few mouthfuls of food he would double up with pain, become deathly pale, and have to lie down for a short while to gradually recover."

On physical examination the patient was pale and undernourished; the oral temperature was 100.2; his abdomen distended but without localized tenderness or palpable masses. The Mantoux test was negative and his leucocyte count was moderately elevated. A *gastro-intestinal X-ray study* was non-informing; repeated examinations of the urine made renal colic improbable.

After several weeks of observation and treatment by rest, a careful dietetic regimen, and good elimination, which failed to alter the condition of affairs, an exploratory laparotomy was done based upon a tentative diagnosis of chronic mesenteric lymphadenitis. Large masses of glands, matted together by adhesions, were found. One of them was removed for biopsy and a normal looking appendix was removed. There was no caseation or tubercle formation in the gland and the pathologist reported "a non-tuberculous inflammatory process." The boy made a good post-operative and subsequent clinical recovery.

*Case 2.*—In many ways this was similar to the first; a girl, age four, whose mother, prior to marriage, had been operated upon for tuberculous peritonitis. This child ran a slight fever, had mild attacks of colic, but nothing comparable with the agonizing pain of the boy just described. Her chief symptom was vomiting; this had occurred of late associated with anorexia, considerable loss of weight, extreme abdominal distension and increasing pallor. The intra-cutaneous tuberculin tests in increasing concentration uniformly were negative, which did not convince her mother that the child's condition was in any wise different from what she herself had experienced during her girlhood. It was chiefly through the mother's insistence that a laparotomy was performed. A non-tuberculous mesen-

teric lymphadenitis was found, a normal appendix removed and this child, like Case 1, made an uneventful post-operative and clinical recovery.

Hyperirritability of the mesenteric nerves as a result of mesenteric adenitis is known to be capable of producing spasm of certain loops of the intestine. Freeman likens this condition to pylorospasm and speculates on the part that such intestinal spasm may play in the mechanism whereby intussusception is produced. Also, he regarded this condition as a potential cause of spastic ileus. Symptoms of obstruction may occur in cases of mesenteric lymphadenitis. Clute and also Wilensky mention the possibility of obstruction of the bowel by adhesions, or by compression due to enlarged mesenteric nodes. Appelmans, in a study of 29 cases of duodenal obstruction, found one case in which the obstruction was caused by the compression of an enlarged lymph node. Davis has reported three cases of compression of the duodenum from lymph nodes in the mesentery. In all three of these cases duodeno-jejunosomy was necessary to relieve the obstruction.

The next two of our cases demonstrate upper intestinal obstruction due to spasm secondary to mesenteric lymphadenitis.

*Case 3.*—A child when two months old was first seen because of vomiting. He had been breast fed for 6 weeks and then had been put on a nutrient formula. The vomiting began during the breast feeding period and had grown worse on artificial feeding. The boy's rectal temperature consistently was a somewhat over 100° F. His abdomen exhibited visible peristalsis, but no tumor could be felt and at no time, during the period of medical treatment for what was diagnosed as pylorospasm, did the patient pass "starvation stools". He retained food with the aid of atropine, lavage and refeedings sufficiently adequate to enable him to gain slightly in weight. By the time the lad was 5 months old however, all concerned were so discouraged with his lack of progress that they were willing to attempt relief by surgical intervention. A marked mesenteric adenitis was found. Associated with it, however and with no demonstrable lesion at the pylorus, the surgeon described a moderate dilatation of the duodenum and a spasticity of the jejunum and upper ileum. The post-operative course was uneventful, but his clinical condition was in no way improved. Vomiting continued and within a few weeks after operation became "bilious". Huge amounts of bile stained fluid were vomited every few days. At the age of 8 months a gastro-enterostomy was done with a view to side-tracking the dilated duodenum. At the second operation the mesenteric adenitis had not changed from the condition found previously. During the following months the patient's abdomen was daily exposed to ultra-violet radiation and several X-ray exposures in an endeavor to influence the mesenteric adenitis. He gradually improved, but it is difficult to decide whether or no the therapy he received influenced his recovery.

*Case 4.*—A 5 months' old baby who had never done well. This infant vomited both when on breast and artificial feeding. The baby cried a lot and had a slight fever most of the time. The abdomen exhibited marked visible peristalsis; as was Case 3, this patient likewise was diagnosed, pylorospasm. The child was put on thick cereal feedings and luminal but without improvement of its condition. In an effort more accurately to make a diagnosis, barium meal was given; this showed that there was no pyloric obstruction, but actually a very marked gastric hyperperistalsis which rushed the meal through the stomach and duodenum only to have it meet what seemed to be a real obstruction in the upper ileum. Immediate operation was advised. The family procrastinated but was willing to leave

the baby in the hospital for the administration of fluids, parenterally. This was done for 24 hours when the baby's abdomen became tremendously distended and the patient passed into collapse. When seen within a quarter of an hour of this occurrence it was obvious that the infant had suffered an acute gastric dilatation. A tube was inserted and an enormous amount of fluid was aspirated from its stomach. The subject's condition improved, but the dire catastrophe just averted served to bring about the family's ready acquiescence to surgery. Under local anesthesia the abdomen was opened. A spastic ileum, associated with a very marked and widespread mesenteric adenitis, was found but no other lesion. There were no congenital peritoneal bands or adhesions, or any pathology other than that described to account for the condition. Post-operatively, the baby was transfused and parenteral fluids were administered. Its stomach however, never regained normal motor function. Food introduced by gavage could be removed hours later supplemented by great amounts of fluid which had collected in the stomach. At autopsy no pathology other than that found at operation could be demonstrated. The adenitis was of the non-tuberculous type; gross and microscopic examination of the intestinal wall showed nothing pathological.

Most writers on the subject of mesenteric lymphadenitis call attention to the readiness with which the condition can be confused with acute appendicitis. McFadden attempts to point out a distinguishing characteristic in the localization of tenderness. He says that in mesenteric adenitis the point of maximal tenderness is not at McBurney's point, but is higher and more medial. Also he states that the lateral, sacral glands often are involved and may be felt along the lateral wall of the pelvis on rectal examination. Recently Karger has described a method of deep "gliding palpation" in which the abdominal contents are palpated against the spinal column. This, he claims, enables one to determine the presence or absence of enlarged abdominal lymph nodes. None of these suggestions has proven of particular helpfulness in the personal experience of the Authors. The two instances which follow are recent ones in which the diagnosis of acute appendicitis definitely was made and at operation acute lymphadenitis was found.

*Case 5.*—A girl of 12 was seen in the evening of a day that illness had been ushered in by chilliness and nausea; these symptoms followed by vomiting and acute abdominal pain. Her oral temperature was 102° F. She was definitely tender in her right lower quadrant and her right rectus muscle was rigid. A moderate leucocytosis was recorded. There was no preoperative doubt of a diagnosis of acute appendicitis and no hesitation in recommending surgery. At operation however, the appendix proved to be long but otherwise normal but about the ileo-cecal junction was a mass of swollen, reddened, discrete and soft mesenteric glands. The child recovered without incident. The glands histologically were negative for tuberculosis.

*Case 6.*—A girl of 12, gave a history of recurrent attacks of abdominal pain for several months; these were associated with anorexia, fever and vomiting. The attack in which she was seen had had its onset a few hours before and was more severe than had been any previous experience. Her physical signs were sufficiently typical to warrant concurrence with the attending physician's diagnosis of appendicitis. The appendix undoubtedly was the scene of previous conflict. It was bound to the cecum by dense adhesions but was not acutely inflamed and it is doubtful if it played any part in the production of the symptomatology which led to laparotomy. There was a group of acutely inflamed mesenteric nodes in the ileo-

cecal angle which probably were the cause of the acute abdominal upset. These glands showed only simple inflammatory changes on microscopic examination.

*Case 7.*—Demonstrates a different type of mesenteric adenitis in which there were unusual complications. The patient, a boy age 6, was admitted to the hospital for a study of his asthma. Almost a month after admission he, as were six other children on the ward, was seized with a febrile illness associated with abdominal pain and leucocytosis. The other children never presented definite physical signs other than fever and all recovered after three or four days. All were diagnosed as influenza with abdominal symptoms due to mesenteric lymphadenitis. This particular patient, however, continued to have symptoms. His abdomen was distended and generally tender, but at first without localization of pain or tenderness. Vomiting was frequent. The temperature was at first remittent in type and the rises were occasionally associated with chills. After the first few days the temperature became more constant and reached 105.6° F. On the tenth day, the abdominal pain became more severe and the patient looked considerably worse; a firm, tender mass was palpable in the right lower quadrant. He was operated upon with a tentative diagnosis of appendiceal abscess. At first a McBurney incision was made but the cecum could not be found. A small loop of inflamed intestine was delivered. A large mass then was palpable toward the mid-line. A right rectus incision next was made and after considerable difficulty the small bowel was freed from a mass of adhesions. It was markedly inflamed and was very thick and leathery in consistency. A large mesenteric node was found; evidently this had suppurated and had become surrounded by a thick exudate. All of the mesenteric vessels examined were thrombosed. No gangrenous bowel was noted. The abdomen was closed with ample drainage; the child recovered after a stormy convalescence. Since that time he has been free from marked abdominal symptoms although he has occasional abdominal cramps. Otherwise he is well and in good nutritional condition.

This case demonstrates several important features of the clinical and pathological picture of mesenteric lymphadenitis. It is an extremely variable syndrome and may be a serious one. Case 7 illustrates, first, that mesenteric lymphadenopathy may complicate an inflammatory disease of the intestinal wall itself, in this instance regional ileitis. The lymph nodes may, but fortunately do not often, suppurate. Peritonitis may result in those cases in which the nodes break down. Whether mesenteric adenitis may be one of the underlying factors in the etiology of so called idiopathic peritonitis is a question which cannot be answered. Another possible pathologic complication of mesenteric lymphadenitis, which was demonstrated by Case 7, was mesenteric thrombosis.

#### COMMENT

The surgical importance of mesenteric lymphadenitis has been stressed by almost all writers whose work has been quoted in this report. The advisability of surgical intervention in any instance of intra-abdominal disease which suggests the probability of appendicitis cannot be doubted. Dr. Holt has said, "in appendicitis in children all signs fail". The impossibility of diagnostically eliminating appendicitis in most cases of mesenteric lymphadenitis without a laparotomy would appear to make operation imperative in practically every instance. The responsibility of not operating upon a case of appendicitis because of confusion in this difficult differential diagnosis is too great to be assumed by any physician. A large num-

ber of cases of simple mesenteric adenitis seem to have been cured by simply opening the abdomen. Explanation for the efficacy of this procedure is lacking, but there is much evidence that relief from symptoms occurs following post-operative recovery in definitely non-tuberculous patients.

After-treatment, consisting of general hygienic management, rest and proper diet, and of ultra violet

and X-ray exposures of the abdomen, has been carried out by most physicians who have reported cases of non-tuberculous mesenteric lymphadenitis. Whether the medical care or the surgery has been the beneficial agent in these children may not be stated on the basis of proof. Hence until the diagnosis of non-tuberculous mesenteric lymphadenitis can be made with more certainty than now, surgery must not be withheld.

## REFERENCES

1. Alvarez, W. C.: Mesenteric Lymphadenitis in Adults, a cause of Pseudo-appendicitis, etc. *Med. Cl. N. Am.*, Vol. 14, p. 605, Nov., 1930.
2. Appelmann, Van Goldenshoven, Boine: A Review of the causes of Duodenal compression. *Rev. Belge, dis. Sc. Med.*, Vol. 11, 1930.
3. Bell, Leo P.: Mesenteric Lymphadenitis simulating an acute abdominal condition. *S. G. O.*, Vol. 45-465, 1927.
4. Brown, H. P.: Acute Mesenteric Adenitis simulating Appendicitis. *S. Clin. N. Am.*, Vol. 9, p. 1195, Oct., 1929.
5. Braithwaite, L. R.: Tuberculous glands of the ileo-caecal angle, a cause of pain in the right iliac fossa. *Br. J. Surg.*, Vol. 13, p. 139, 1926.
6. Carson, H. W.: Of the clinical aspects of tuberculous mesenteric glands. *Lancet*, Vol. 1, p. 869, June, 1918.
7. Clute, H. M.: Enlarged Mesenteric Lymph nodes. *Boston M. and S. J.*, Vol. 183, 1920.
8. Cohen, Morris: Acute Surgical Disease of the Abdomen in Children. *S. G. O.*, Vol. 45, p. 595, 1927.
9. Crohn, Burrill B.; Ginzburg, Leon; Oppenheimer, Gordon: Regional Ileitis. *J. A. M. A.*, Vol. 99, p. 1323, Oct., 1932.
10. Davis and Harven: Compression of the Duodenum by Mesenteric nodes. *J. de Chir. et Ann. Soc. Belge, de Chir.*, Vol. 27, p. 268, 1928.
11. Freeman, Leonard: Surgical significance of Mesenteric Lymphadenitis. *S. G. O.*, Vol. 37, 1923.
12. Heuser: Mesenteric Lymphadenitis. *Brit. z Klin. Chir.*, Vol. 130, 1923.
13. Higgins, R. H.: Suppuration in the retroperitoneal space. *S. G. O.*, Vol. 12, 1911.
14. Irwin, S. I.: Hypertrophy of the mesenteric lymph glands. *Lancet*, Vol. 2, p. 1081, Nov., 1931.
15. Karyer, P.: Diagnosis of disorders of the Mesenteric Lymphnodes. *Jahrbuch f. Kinderheilkunde*, Vol. 139, p. 91, 1932.
16. Kiss, F.: Topographic relationship between nerve plexuses and lymph nodes of the abdomen. *Arch. Surg.*, Vol. 21, p. 405-411, Aug., 1930.
17. Lamson, O. F.: Mesenteric lymphadenitis and acute appendicitis. *Surg. Cl. N. Am.*, Vol. 11, p. 1061, Oct., 1931.
18. McFadden: Mesenteric lymphadenitis and its clinical significance. *Br. Med. J.*, Vol. 2, 1927.
19. Strauther, J. W.: Mesenteric lymphadenitis simulating appendicitis. *Edinburgh M. J.*, Vol. 27, 1921.
20. Surg. Clin. N. Am., Vol. 9, Oct., 1929. Acute Mesenteric adenitis simulating appendicitis.
21. Surg. Clin. N. Am., Vol. 4, Feb., 1924. Acute mesenteric adenitis associated with chronic appendicitis.
22. Short, A. Rendle: Symptoms due to Mesenteric Lymphadenitis. *Lancet*, Vol. 2, p. 909, 1928.
23. Speece, John: Mesenteric Adenitis. *Penn. Med. J.*, Vol. 58, 1928, and Vol. 32, 1929.
24. Schnitzler: Mesenteric lymphangitis and adenitis. *Wien. Klin. Woch.*, Vol. 35, p. 134, Feb., 1933.
25. Turberville, J. S.: Two cases of suppuration of the mesenteric lymph nodes. *So. Med. J.*, Vol. 21, p. 475, 1928.
26. Wilensky, A. O.: Mesenteric Lymphadenitis. *Med. Rec.*, Vol. 99, p. 770, 1920.
27. Wilensky, A. O., and Hahn: Mesenteric Lymphadenitis. *Ann Surg.*, Vol. 83, 1926.

## ABSTRACTS

E. S. EMERY, JR., AND R. T. MONROE.

*Peptic Ulcer. A Study of 1435 Cases. Arch. Int. Med.*, 1935, Vol. 55, p. 271.

This study of a large group over a long period shows that the disease tends to persist through life when once established. The cause of ulcer remains unknown. The disease is rarely fatal, and does not generally shorten life, and in the average case does not tend to get worse as time goes on.

None of the present medical or surgical methods of treatment, no matter how strict, do more than help to induce remissions. Surgery produces longer intermissions, but has a definite mortality and mechanical and chemical complications. A plan of treatment is offered to produce the best result at the least cost. Its chief aspect is prevention of a relapse by lessening fatigue, worry and infection. Surgery is used only to close a perforation, to relieve permanent obstruction (with over 40% 6 hour barium residue) to overcome a tendency to bleed, and in cases of suspected malignant degeneration. The patient should have complete medical treatment and follow up after operation. Periods of hypersecretion call for special medical care. Operation at this time is disastrous.

Franklin W. White, Boston.

OTTENBERG, REUBEN.

*Painless Jaundice. J. A. M. A.*, 1935, May 11, 1935.

In the majority of cases of jaundice the diagnosis is not difficult. In the remaining 20 to 30 per cent of the cases, however, there is no laboratory or clinical method of distinguishing whether we are dealing with an obstructive or a toxic type of jaundice.

The history is generally more helpful than the physical examination. The determination of whether bile is enter-

ing the intestinal tract is useful. The author has found the icterus index more accurate than the van den Bergh test in the estimation of the bilirubin of the blood. Extremely high levels of blood bilirubin most commonly occur in hepatic degeneration.

In obstructive jaundice the blood cholesterol is usually high. In hepatic degeneration the blood cholesterol is generally low.

The positive galactose test indicates hepatic degeneration.

The differentiation as to whether the case is a medical or a surgical one is important. Surgery should be done early.

In the medical treatment the high carbohydrate diet seems protective. Reduction of protein in the diet seems to have experimental backing. Drugs are apparently of no importance. Cathartic treatment should not be pushed too vigorously. The use of bile salts and other cholagogues is not advocated.

Francis D. Murphy, Milwaukee.

GARDNER, JR., CLARENCE E., AND HART, DERYL.

*Enterogenous Cysts of the Duodenum. J. A. M. A.*, 1935, May 18, 1935.

The authors report a case of a cyst of the duodenum which was successfully treated surgically by anastomosis between the cyst and the duodenal lumen. The authors review six cases of cysts of the duodenum from the literature. The mortality in these six cases was 100 per cent. No case has been diagnosed before operation or autopsy. Three of the collected cases were treated surgically.

The probable origin of the cyst is from an embryonic diverticulum.

Francis D. Murphy, Milwaukee.

## SECTION II—*Experimental Physiology*

### The Effect of Oxygen Inhalation on Gaseous Distention of the Stomach and the Small Intestine\*

By

JACOB FINE, M.D., JOHN B. SEARS, M.D.

and

BENJAMIN M. BANKS, M.D.

BOSTON, MASSACHUSETTS

IN a previous communication (1) it was demonstrated that nitrogen and hydrogen constitute the major portion of the gases responsible for gaseous distention of the stomach and small intestine. There is urgent need for a more effective method of eliminating these gases than is now available. A possible answer to this problem is suggested in the work of McIver, Redfield and Benedict (2) who found that a loop of small intestine distended with nitrogen can be deflated more rapidly if the animal is allowed to breathe pure oxygen instead of air.\*\* This is attributable to the resulting elimination from the blood of the nitrogen dissolved in it, thus permitting diffusion of this gas from the intestine into the blood in accordance with the law that, other things being equal, the rate of diffusion of a gas across a semi-permeable membrane is proportional to the difference in the partial pressure of the gas on the two sides of the membrane.

The present study comprises an extended series of observations along similar lines for the purpose of establishing a broader basis for the application of this principle to the clinical condition of intractable distention.

#### METHOD

Cats were starved for a minimum of 24 hours so that the stomachs and the small intestines were found free of gas and fluids when the experiments were started. Through an abdominal incision under nembutal anesthesia a ligature was placed around the cardia, pylorus and ileocecal valve without disturbing the circulation. The entire stomach or small intestine or both, if empty and collapsed, were then inflated by means of a gas-filled leak-proof syringe and needle with a carefully measured volume of gas sufficient to produce moderate or severe distention. The hole made by the needle was effectively sealed by squeezing the gut between the fingers. The abdomen was closed. "Commercially pure" oxygen was then supplied under atmospheric pressure through a tracheal cannula connected with one way Tissot valves for inspiration and expiration. After periods varying from six to twenty-four hours the

animals were sacrificed and the residual gases removed, measured and, in some instances, analyzed by means of the Van Slyke manometric apparatus with an attached combustion chamber for hydrogen determinations. The results were compared with controls treated in the same way but breathing air instead of oxygen.

When the empty gastro-intestinal tract is inflated with a pure gas, diffusion of other gases ( $\text{CO}_2$ ,  $\text{O}_2$  and  $\text{N}_2$ ) from the blood into the intestine immediately takes place, so that the residual gas removed at the end of any given period is a mixture of gases. In the subsequent text it will therefore be necessary to distinguish between the change in *total gas volume* and that of the pure gas originally injected.

#### RESULTS

1. *A comparison of the effect of breathing pure oxygen with that of air on the change in total gas and nitrogen volume in the small intestine distended with nitrogen and ligated at the pylorus and ileocecal valve—Table I, Figure I.*

The small intestines of four cats were inflated with volumes of nitrogen varying from 75 to 130 c.c. The cats then breathed 100% oxygen for approximately six hours. The residual gas volumes were 67, 74, 81, and 88 percent respectively. For corresponding control animals of equal weight and approximately equal volume of injected gas, but breathing room air, the results were 82, 106, 112, and 109 percent respectively. Oxygen inhalation for six hours, therefore, caused an average decrease in total gas volume of 18% as compared with an average increase of 2% when the animal breathed air.\* From analyses of intestinal gases made by other observers (2) and from several listed in Table I it appears that about 90% of the residual gas is nitrogen, the remainder being nearly entirely oxygen and carbon dioxide. The residual volume of nitrogen is therefore some 10% less than these figures for total gas volume. In terms of nitrogen the average decrease equalled 26.2% in the "oxygen cats", as compared with 8.2% in the "air cats", or an acceleration in the rate of nitrogen absorption of 320% as a result of the use of oxygen.

\*From the Surgical Laboratory of the Beth Israel Hospital and the Harvard Medical School, Boston, Massachusetts. The expenses of this investigation were provided by the DeLamar Mobile Research Fund, Harvard Medical School.  
Submitted April 3, 1935.

\*\*Thus in a 30 cm. loop of small intestine containing 20 c.c. of nitrogen, 7.5 c.c. were absorbed in 6 hours if the animal breathed air as compared with 10.2 c.c. if the animal breathed pure oxygen.

\*This increase is due to the diffusion of oxygen and carbon dioxide from the blood into the gut in greater volume than of nitrogen out of the gut into the blood.

TABLE I

*The Effect of Breathing Oxygen vs. Air on the Change in Gas Volume in the Small Intestine Distended With Nitrogen*

| Exp. No. | Wt. of Cats* in Kilos | Duration of Experiment in Hours | Volume of Nitrogen Injected in cc. |         | Residual Gas Volume in cc. |         | Residual Gas Volume in % |         | Average Decrease in Total Gas Volume |         | Average Decrease in Nitrogen Volume in %** |         | Remarks                                                                                                                                                                                                                                             |
|----------|-----------------------|---------------------------------|------------------------------------|---------|----------------------------|---------|--------------------------|---------|--------------------------------------|---------|--------------------------------------------|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|          |                       |                                 | Oxygen Cat                         | Air Cat | Oxygen Cat                 | Air Cat | Oxygen Cat               | Air Cat | Oxygen Cat                           | Air Cat | Oxygen Cat                                 | Air Cat |                                                                                                                                                                                                                                                     |
| 31       | 2.3                   | 5½                              | 130                                | 130     | 114                        | 146     | 88                       | 112     |                                      |         |                                            |         | Oxygen 3 hrs. on—2 hrs off                                                                                                                                                                                                                          |
| 40       | 3.0                   | 6                               | 105                                | ...     | 85                         | ...     | 87                       | ...     |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 18       | 3.8                   | 6                               | 100                                | 100     | 94                         | 109     | 94                       | 109     |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 19       | 2.4                   | 6                               | 75                                 | 75      | 61                         | 80      | 81                       | 106     |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 30       | 2.7                   | 7                               | 117                                | 137     | 78                         | 113     | 67                       | 82      | 18                                   | ***     | 26.2                                       | 8.2     | Oxygen 3 hrs. on—1 hr. off<br>Oxygen 3 hrs. on—1 hr. off                                                                                                                                                                                            |
| 38       | 3.0                   | 11                              | 100                                | 100     | 48                         | 78      | 48                       | 78      |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 48       | 2.0                   | 11                              | 100                                | ...     | 74                         | ...     | 74                       | ...     |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 20       | 2.0                   | 12                              | 75                                 | 100     | 40                         | 101     | 53                       | 100     |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 33       | 2.5                   | 12                              | 100                                | 100     | 66                         | 100     | 66                       | 100     |                                      |         |                                            |         | Oxygen 3 hrs. on—½ hr. off                                                                                                                                                                                                                          |
| 37       | ?                     | 12                              | 100                                | 100     | 62                         | 80      | 62                       | 80      |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 44       | 3.8                   | 12                              | 140                                | 100     | 82                         | ...     | 59                       | 78      |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 45       | 3.4                   | 12                              | 140                                | ...     | 73                         | ...     | 52                       | ...     |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 47       | 2.0                   | 12                              | 100                                | ...     | 64                         | ...     | 64                       | ...     |                                      |         |                                            |         | Oxygen 3 hrs. on—1 hr. off<br>Oxygen 3 hrs. on—1 hr. off<br>Oxygen 3 hrs. on—1 hr. off                                                                                                                                                              |
| 49       | 2.0                   | 12                              | 100                                | ...     | 63                         | ...     | 63                       | ...     |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 50       | 2.8                   | 11                              | 125                                | 100     | 76                         | 90      | 61                       | 90      | 39.8                                 | 13.1    | 44.9                                       | 21.1    |                                                                                                                                                                                                                                                     |
| 5        | 3.8                   | 17                              | 150                                | ...     | 50                         | ...     | 33                       | ...     |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 32       | 2.4                   | 18                              | 100                                | 100     | 39                         | 92      | 39                       | 92      |                                      |         |                                            |         | Gas analysis<br>CO <sub>2</sub> O <sub>2</sub> N <sub>2</sub><br>{ O <sub>2</sub> Cat 10.6 5.7 83.7<br>Air Cat 7.9 0 92.1<br>{ O <sub>2</sub> Cat 9.4 2.0 88.6<br>Air Cat 11.6 0.8 86.9<br>O <sub>2</sub> Cat 8.3 1.9 90.7<br>Air Cat 11.9 1.8 86.3 |
| 34       | 3.2                   | 18                              | 125                                | 125     | 67                         | 113     | 54                       | 90      |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 35       | 2.6                   | 20                              | 100                                | ...     | 54                         | ...     | 54                       | ...     | 55.0                                 | 9.0     | 59.5                                       | 18.1    |                                                                                                                                                                                                                                                     |
| 4        | 3.6                   | 22                              | 124                                | 146     | 40                         | 174     | 32                       | 119     |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 6        | 4.1                   | 22                              | 125                                | 125     | 40                         | 116     | 32                       | 93      |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 9        | 3.7                   | 22                              | 150                                | 150     | 33                         | 100     | 52                       | 148     |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 7        | 3.7                   | 24                              | 150                                | 190     | 89                         | 195     | 59                       | 106     |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 11       | 4.3                   | 24                              | 130                                | 85      | 58                         | 54      | 45                       | 64      |                                      |         |                                            |         |                                                                                                                                                                                                                                                     |
| 14       | 3.4                   | 24                              | 150                                | 150     | 75                         | 146     | 50                       | 98      | 59.2                                 | 3.4     | 62.3                                       | 12.9    |                                                                                                                                                                                                                                                     |

\*Approximately same weight for both cats in each experiment.

\*\*Calculated on basis of gas analyses in Exp. 9, 11 and 14 and from data in literature showing that residual volume of nitrogen constitutes approximately 80% of the total gas volume.

\*\*\*2% increase due to diffusion of O<sub>2</sub>, CO<sub>2</sub>, and N<sub>2</sub> from the blood into the intestine. See gas analyses in column labelled remarks.

When the same experiments were repeated for periods of 12, 18, and 24 hours the percentage absorption of total gas and nitrogen volume increased with the time.

In summary the results show that:

(a) In cats breathing air the total gas volume in the small intestine is reduced 13.1% within 12 hours. During the subsequent twelve hours however diffusion of gases from the blood into the intestine apparently exceeds absorption of gases from the intestine into the blood because the reduction in total gas volume equals only 3.4% after 24 hours.

(b) On the other hand, in cats breathing oxygen a progressive decline in total gas volume in the small intestine occurs until a maximum reduction averaging 59.2% is reached in 24 hours.

(c) When air is breathed, the average decrease in volume of nitrogen in the small intestine after 12 hours equals 21.1%. After 24 hours this decrease equals only 12.9%.

(d) When oxygen is breathed, an average of 44.9% of the nitrogen in the small intestine is absorbed dur-

ing the first twelve hours. An additional 17.4% disappears in the succeeding twelve hours.

The advantage of breathing pure oxygen over air for the reduction of total gas and nitrogen volume in the small intestine is therefore obvious.

2. A comparison of the effect of breathing pure oxygen with that of air on the change in total gas and nitrogen volume in the stomach distended with nitrogen and ligated at the cardia and pylorus—Table II, Figure II.

The observations under this heading were made simultaneously with those on the small intestine described in section I. The duration of the experiments and the amounts of nitrogen used were as a rule the same. In Table II it will be observed that the total gas volume in the stomach was (excluding two notable exceptions\*) approximately the same after periods vary-

\*In experiments 5 and 9 a huge increase in volume occurred (237.4% and 173.3%, respectively). The ligatures at the cardia and pylorus were intact. Analysis of the gases showed the usual percentages of O<sub>2</sub>, CO<sub>2</sub>, and N<sub>2</sub>. Whether these results constitute examples of the phenomenon of acute dilatation of the stomach is uncertain. A deliberate effort to produce this condition by over-distention of the stomach failed on two occasions in average sized cats, once with the use of 175 c.c. of nitrogen and again with 320 c.c.



TABLE II

*The Effect of Breathing Oxygen vs. Air on the Change in Gas Volume in the Stomach Distended With Nitrogen*

| Exp. No. | Wt. of Cats* in kilos | Duration of Experiment in Hours | Volume of Nitrogen Injected in cc. |         | Residual Gas Volume in cc. |         | Residual Gas Volume in % |         | Average Change in Total Gas Volume in % |         | Average Decrease in Nitrogen Volume in % |         | Remarks                                       |
|----------|-----------------------|---------------------------------|------------------------------------|---------|----------------------------|---------|--------------------------|---------|-----------------------------------------|---------|------------------------------------------|---------|-----------------------------------------------|
|          |                       |                                 | Oxygen Cat                         | Air Cat | Oxygen Cat                 | Air Cat | Oxygen Cat               | Air Cat | Oxygen Cat                              | Air Cat | Oxygen Cat                               | Air Cat |                                               |
| 37       | 2.3                   | 5½                              | 100                                | 100     | 98                         | 103     | 100                      | 103     |                                         |         |                                          |         |                                               |
| 40       | 3.0                   | 6                               | 89                                 | ...     | 95                         | ...     | 106                      | ...     |                                         |         |                                          |         |                                               |
| 18       | 3.8                   | 6                               | 75                                 | 75      | 84                         | 86      | 100                      | 102     |                                         |         |                                          |         |                                               |
| 19       | 2.4                   | 6                               | 75                                 | 75      | 75                         | 80      | 100                      | 106     |                                         |         |                                          |         |                                               |
| 30       | 2.7                   | 7                               | 100                                | 100     | 94                         | 95      | 94                       | 95      | 0.0                                     | +1.5    | 10.0                                     | 8.7     |                                               |
| 38       | 3.0                   | 11                              | 100                                | ...     | 110                        | ...     | 110                      | ...     |                                         |         |                                          |         |                                               |
| 20       | 2.9                   | 12                              | 75                                 | 75      | 76                         | 82      | 101                      | 109     |                                         |         |                                          |         |                                               |
| 33       | 2.5                   | 12                              | 100                                | 100     | 102                        | 106     | 102                      | 106     |                                         |         |                                          |         |                                               |
| 37       | ?                     | 12                              | 100                                | 100     | 97                         | 108     | 97                       | 108     | +2.5                                    | +7.3    | 7.8                                      | 3.4     |                                               |
| 5        | 3.8                   | 17                              | 125                                | 125     | 320                        | 152     | (256**)                  | 122     |                                         |         |                                          |         |                                               |
| 32       | 2.4                   | 18                              | 100                                | 100     | 90                         | 100     | 90                       | 100     |                                         |         |                                          |         |                                               |
| 34       | 3.2                   | 18                              | 125                                | ...     | 104                        | ...     | 83                       | ...     |                                         |         |                                          |         |                                               |
| 35       | 2.6                   | 20                              | 64                                 | 84      | 65                         | 90      | 101                      | 107     | -9.3                                    | +9.6    | 17.5                                     | 1.4     |                                               |
| 4        | 3.6                   | 22                              | 150                                | 144     | 150                        | 122     | 100                      | 85      |                                         |         |                                          |         | Gas analysis                                  |
| 6        | 4.1                   | 22                              | 125                                | 125     | 125                        | 154     | 100                      | 123     |                                         |         |                                          |         | CO <sub>2</sub> O <sub>2</sub> N <sub>2</sub> |
| 9        | 3.7                   | 22                              | 150                                | 150     | 260                        | 158     | (173**)                  | 105     |                                         |         |                                          |         | { O <sub>2</sub> Cat 9.8 1.2 89.0             |
| 7        | 3.7                   | 24                              | 125                                | 125     | 134                        | 150     | 107                      | 120     |                                         |         |                                          |         | { Air Cat 8.8 0.2 91.0                        |
| 11       | 4.3                   | 24                              | 125                                | 95      | 144                        | 105     | 115                      | 110     |                                         |         |                                          |         | { O <sub>2</sub> Cat 6.5 1.3 92.2             |
| 14       | 3.4                   | 24                              | 100                                | 100     | 100                        | 110     | 100                      | 100     | +4.5                                    | +8.8    | 6.0                                      | 1.4     | { O <sub>2</sub> Cat 9.0 0.8 89.2             |
|          |                       |                                 |                                    |         |                            |         |                          |         |                                         |         |                                          |         | { Air Cat 5.2 1.3 93.5                        |
|          |                       |                                 |                                    |         |                            |         |                          |         |                                         |         |                                          |         | { Air Cat 7.9 1.5 90.6                        |

\*Approximately same weight for both cats in each experiment.

\*\*Anomalous results not included in average figures in next column—see footnote in subsequent text.

\*\*\*Calculated on basis of gas analysis in Exp. 9, 11, and 14 and from data in literature showing that residual volume of nitrogen constitute approximately 90% of the total gas volume.

ing from 6-24 hours as at the beginning and that this was the case whether air or oxygen was used. Indeed, in many instances a little more gas was recovered than was injected. Cats breathing oxygen however usually had a somewhat smaller residual volume than those breathing air. Except for Experiments 5 and 9 the absorption of nitrogen averaged about 10.3% in the "oxygen cats" and 3.9% in the "air cats". Oxygen accelerates the rate of absorption of nitrogen from the stomach 260%, but the decrease in nitrogen volume is negligible even when oxygen is used as the respiratory gas. The stomach is therefore of no consequence as an organ for the absorption of nitrogen.

The relative capacity of the stomach and small intestine for the absorption of nitrogen and the reduction of total gas volume is however very considerable, particularly when oxygen is used as the respiratory gas. Thus when air is breathed, the absorption of nitrogen from the small intestine at the end of 24 hours is 6% and from the stomach 2.1%, a ratio of 2.85. When oxygen is breathed the corresponding figures are 62.3% and 6%, a ratio of 10.4.

3. *A comparison of the effect of breathing pure oxygen with that of air on the gaseous exchange in the stomach and small intestine separately distended with pure hydrogen.*

An examination of the data in Tables III and IV permits the following conclusions:

(a) When the small intestine of an air-breathing cat is inflated with hydrogen, the percentage reduction

of total gas volume after a given period is very much greater than is the case when the intestine is inflated with nitrogen. This is due to the fact that hydrogen has a much higher diffusibility coefficient than nitrogen, as already observed by others.

(b) The inhalation of oxygen in place of air considerably increases the percentage reduction of total gas volume in the small intestine (Figure III).

(c) When the stomach of an air-breathing cat is inflated with hydrogen the total gas volume is reduced to a very much smaller extent than in the small intestine. In the stomach no material change in the total gas volume is effected by oxygen (Figure IV).

(d) These findings are similar to those obtained when nitrogen is used as the distending gas, but upon consideration of the data in the gas analyses in Tables III and IV it will be seen that the mechanism involved is not the same. In experiment 21, for example, in the cat breathing oxygen, 68.3% of the initial volume of hydrogen was absorbed from the small intestine while 80.7% was absorbed in the cat breathing air. On the other hand in the "oxygen cat" only 4.5 c.c. of nitrogen diffused into the intestine from the blood as compared with 43 c.c. in the "air cat". In the stomach of the "oxygen cat" the percentage absorption of hydrogen was 19.4% and in the "air cat" 45.2%. Only 3.4 c.c. of nitrogen entered the stomach from the blood in the former while 25.9 c.c. entered in the latter. Accordingly it appears that the absorption of hydrogen from the stomach and small intestine is at

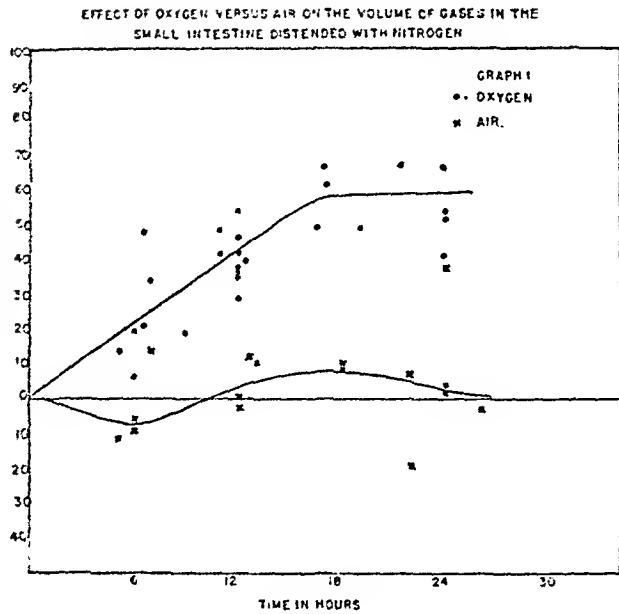


Fig. 1

least as efficient in the cat breathing air as in the cat breathing oxygen\*. Nevertheless, by preventing the diffusion of nitrogen into the gastro-intestinal tract from the blood, oxygen accomplishes, as already stated, a greater eventual decrease in *total gas volume* in the small intestine.

### DISCUSSION

According to the foregoing data, oxygen must be used for at least 12 hours to secure a substantial reduction in the total gas volume in the small intestine originally distended with nitrogen. Shaw and Behnke (3), in experiments on man, have found that about sixty percent of the nitrogen in the blood and tissues is exhaled within the first hour of inhalation of pure

\*Indeed, it would seem from the data in Experiments 21, 60, and 61, in which the analyses are complete, that the inhalation of oxygen actually retards the diffusion of hydrogen from the stomach.

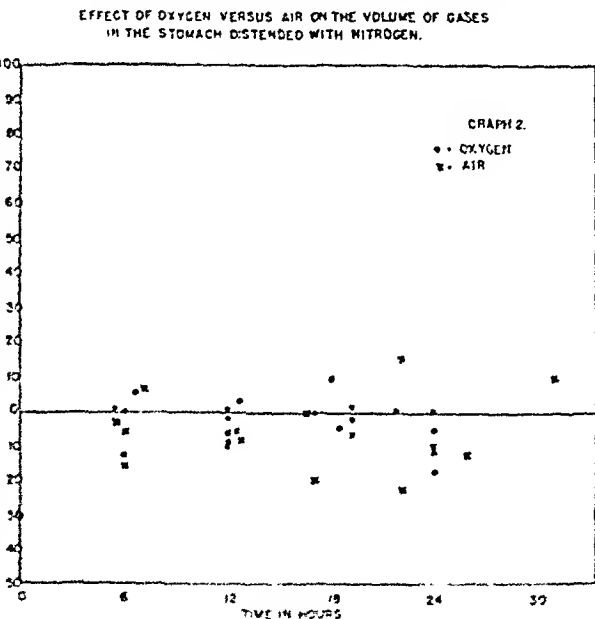


Fig. 2

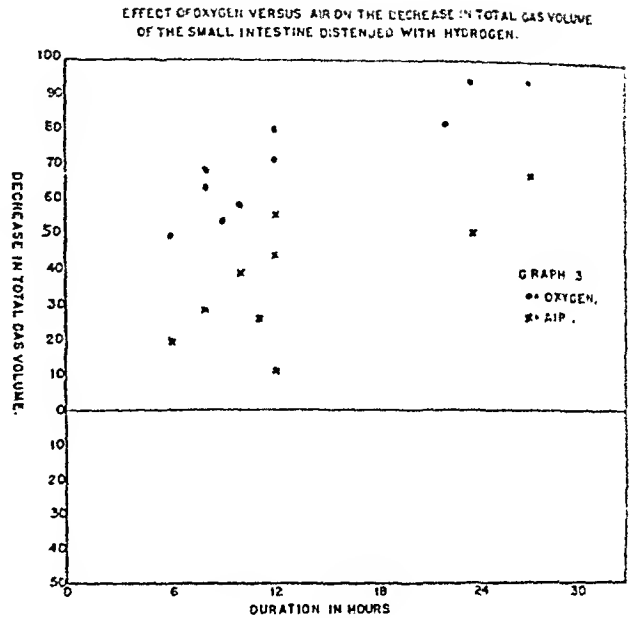


Fig. 3

oxygen. But such a rapid removal of nitrogen from the intestine cannot be expected owing to the fact that the nitrogen in the blood and tissues is in physical solution, while in the intestine nitrogen exists as a gas bubble only the periphery of which is exposed to an absorbing surface.

The absorption of nitrogen from the stomach is so poor, even when oxygen is breathed, that its disposal for the most part can only be accomplished by regurgitation into the oesophagus, or by evacuation into the small intestine.

The striking difference between the stomach and small intestine in the absorption of nitrogen can be explained on the basis of the following considerations. The rate of diffusion of a gas across a semi-permeable membrane is governed by (a) the nature of the mem-

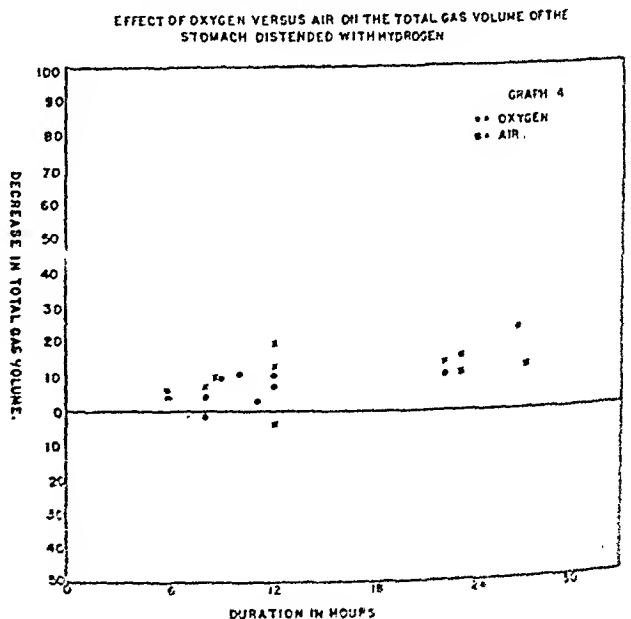


Fig. 4

TABLE III

*The Effect of Breathing Pure Oxygen vs. Air on the Change in Gas Volume in the Small Intestine Distended With Hydrogen*

| Exp. No. | Wt. of Cat* in Kilos | Duration of Experiment in Hours | Volume of Hydrogen Injected in cc. |         | Residual Gas Volume in cc. |         | Decrease in Gas Volume in % |         | Residual Volume of Hydrogen in cc. |         | Decrease in Volume of Hydrogen in % |         | Volume of Nitrogen Diffused into Small Intestine from Blood in cc. |         | Remarks                                                                                  |
|----------|----------------------|---------------------------------|------------------------------------|---------|----------------------------|---------|-----------------------------|---------|------------------------------------|---------|-------------------------------------|---------|--------------------------------------------------------------------|---------|------------------------------------------------------------------------------------------|
|          |                      |                                 | Oxygen Cat                         | Air Cat | Oxygen Cat                 | Air Cat | Oxygen Cat                  | Air Cat | Oxygen Cat                         | Air Cat | Oxygen Cat                          | Air Cat | Oxygen Cat                                                         | Air Cat |                                                                                          |
| 22       | 2.7                  | 6                               | 100                                | 100     | 51                         | 82      | 49                          | 18      | ....                               | ....    | ....                                | ....    | ...                                                                | ....    | CO. O <sub>2</sub> H <sub>2</sub> N <sub>2</sub><br>O <sub>2</sub> Cat 14.0 8.7 67.9 9.4 |
| 65       | 3.0                  | 8                               | 100                                | ...     | 32                         | ..      | 68                          | ..      | 21.7                               | ....    | 78.3                                | ....    | 3.0                                                                | ....    |                                                                                          |
| 63       |                      | 8                               | 100                                | 100     | 38                         | 72      | ..                          | ..      | ....                               | ....    | ....                                | ....    | ..                                                                 | ...     | O <sub>2</sub> Cat 12.8 4.0 73.0 10.2<br>Air Cat . . . . .                               |
| 64       | 4.2                  | 9                               | 100                                | 100     | 47                         | 63      | 53                          | 37      | 34.3                               | ....    | 65.7                                | ....    | 4.75                                                               | ....    |                                                                                          |
| 21       | 3.4                  | 11                              | 100                                | 100     | 42                         | 74      | 58                          | 26      | 31.7                               | 19.3    | 68.3                                | 80.7    | 4.5                                                                | 43.1    | { O <sub>2</sub> Cat 13.4 0.5 75.4 10.7<br>Air Cat 13.5 2.1 26.2 58.2                    |
| 16       | 3.8                  | 12                              | 150                                | 100     | 42                         | 56      | 72                          | 44      | ....                               | 6.3     | ...                                 | 88.8    | ...                                                                | 45.2    |                                                                                          |
| 60       | 3.5                  | 12                              | 100                                | 100     | 20                         | 44      | 80                          | 56      | 17.0                               | 19.1    | 83.0                                | 80.9    | 2.64                                                               | 18.5    | { O <sub>2</sub> Cat 3.0 3.3 80.5 13.2<br>Air Cat 7.8 6.7 43.6 42.0                      |
| 67       | 3.3                  | 12                              | 100                                | 100     | 14                         | 54      | 86                          | 46      | 9.5                                | 14.2    | 91.5                                | 85.8    | 2.56                                                               | 32.9    |                                                                                          |
| 12       | 2.0                  | 22                              | 100                                | ...     | 18                         | ..      | 82                          | ..      |                                    |         |                                     |         |                                                                    |         | { O <sub>2</sub> Cat 7.4 6.8 67.5 18.3<br>Air Cat 6.5 6.2 26.3 61.0                      |
| 17       | 2.6                  | 23                              | 100                                | 100     | 6                          | 50      | 94                          | 50      |                                    |         |                                     |         |                                                                    |         |                                                                                          |
| 10       | 3.0                  | 27                              | 115                                | 125     | 8                          | 40      | 94                          | 68      |                                    |         |                                     |         |                                                                    |         |                                                                                          |

\*Approximately same weight for both cats in each experiment.

brane, (b) its thickness, (c) the pressure of the gas on the two sides of the membrane and (d) the surface area available for absorption.

If the mucosa of the stomach and intestine is regarded as a physical barrier to the passage of gases rather than as a chemically secreting and absorbing membrane, it is probably safe, on the basis of anatomical structure, to consider the first two factors the same for both.

The third factor is not likely to be exactly the same for both since a given gas volume may produce different intraluminal tensions in the stomach and small intestine. We did not measure the gas pressure following injection because we felt that the variability of muscle tonus from time to time in the same animal and from one animal to another would make a single determination meaningless. We were however impressed by the greater resistance to the injection of the last fraction of the same gas volume in the small intestine than in the stomach. The initial pressure in the small intestine was therefore probably greater than in the stomach. That this might account to some extent for the greater speed of absorption from the small intestine cannot be denied. Nevertheless the data of Tables I and II demonstrate beyond reasonable doubt that the tension created by the injected gas cannot be responsible for more than a fraction of the difference actually observed. For example, in Experiments 4 and 14 of Table II the stomachs of two cats of nearly equal weight and breathing oxygen were injected with a nitrogen volume of 150 c.c. and 100 c.c. respectively. The residual total gas volumes remained unaltered after 22 and 24 hours respectively and the percentage absorption of nitrogen was 10% in both instances. Similarly in Experiments 33 (cat wt. 2.5 kilos) and 20 (cat wt. 2.9 kilos) with injected volumes of 100 c.c. and 75 c.c. respectively the absorption of nitrogen from the stomach after twelve hours equalled 8.2% in the former and 9.1% in the latter. In experiments 20 and 45 of Table I the small intestine of two oxygen-breathing cats weighing 2.9 and 3.4 kilos respectively was injected with nitrogen volumes of 75

c.c. and 140 c.c. respectively. In proportion to weight the latter probably had a much greater initial intraluminal tension, but after twelve hours the absorption of nitrogen was about the same in both instances (52 and 53 percent respectively). A comparison of the data of two six-hour oxygen experiments (Exp. 19 and 31) illustrates the same point. Hence the initial difference in intraluminal tensions between the stomach and small intestine cannot be regarded as an adequate explanation for the marked difference in the absorption of nitrogen from these two organs.

Reliable data on the relative surface areas of the stomach and small intestine is meagre. Custor (4) and Sappey (5) have reported figures which fail to take adequate account of the valvulae conniventes. Dargein's (6) direct measurements of the internal surface of the moderately distended adult human duodenum and stomach (110 c.c. water in the duodenum, 1200 c.c. in the stomach) were 432 and 700 square centimeters respectively. If, on the basis of length, the duodenum is estimated to represent 1-18 of the total internal surface of the small intestine, the latter may then be considered to have a surface area fourteen times ( $\frac{432 \text{ cm}^2 \times 18}{700 \text{ cm}^2}$ ) that of the stomach. But calculated on a basis of surface area per unit volume of fluid the ratio is  $6.72 \left( \frac{700}{1200} \right)$  or  $0.583 \text{ cm}^2$  of surface area per cubic centimeter for the stomach,  $\frac{432}{110}$  or  $3.92 \text{ cm}^2$  per cubic centimeter for the duodenum;  $\frac{3.92}{0.583} = 6.72$ . If these ratios apply to the cat as well, their average is sufficiently large to account for the observed differences (Table I and II) in nitrogen absorption between the stomach and small intestine on a surface area basis.

When pure hydrogen is utilized as the distending agent the inhalation of pure oxygen effects a substantially greater decrease in *total gas volume* in the small intestine than occurs when air is breathed. This is not due to an increase in the rate of diffusion of hydrogen from the gastro-intestinal tract as a result of the use of oxygen. The gas analysis data in Tables V and VI show that in an animal breathing air hydrogen

TABLE IV

*The Effect of Breathing Pure Oxygen vs. Air on the Change in Gas Volume in the Stomach Distended With Hydrogen*

| Exp. No. | Wt. of Cat* in Kilos | Duration of Experiment in | Volume of Hydrogen Injected in cc. |         | Residual Gas Volume in cc. |         | Decrease in Gas Volume in % |         | Residual Volume of Hydrogen in cc. |         | Decrease in Volume of Hydrogen in % |         | Volume of Nitrogen Diffused into Small Intestine from Blood in cc. |         | Remarks                                                                                                               |
|----------|----------------------|---------------------------|------------------------------------|---------|----------------------------|---------|-----------------------------|---------|------------------------------------|---------|-------------------------------------|---------|--------------------------------------------------------------------|---------|-----------------------------------------------------------------------------------------------------------------------|
|          |                      |                           | Oxygen Cat                         | Air Cat | Oxygen Cat                 | Air Cat | Oxygen Cat                  | Air Cat | Oxygen Cat                         | Air Cat | Oxygen Cat                          | Air Cat | Oxygen Cat                                                         | Air Cat |                                                                                                                       |
| 22       | 2.7                  | 6                         | 76                                 | 100     | 71                         | 96      | 6.6                         | 4       | ..                                 | ..      | ..                                  | ..      | ..                                                                 | ..      | Gas analysis:<br>CO <sub>2</sub> O <sub>2</sub> H <sub>2</sub> N <sub>2</sub><br>O <sub>2</sub> Cat 11.4 4.5 81.0 3.1 |
| 65       | 3.0                  | 8                         | 100                                | 7       | 100                        | ..      | 0                           | ..      | 82.6                               | ..      | 17.4                                | ..      | 3.16                                                               | ..      |                                                                                                                       |
| 63       | 3.0                  | 8                         | 75                                 | 75      | 72                         | 70      | ..                          | ..      | ..                                 | ..      | ..                                  | ..      | ..                                                                 | ..      | O <sub>2</sub> Cat 8.1 5.1 56.8 0<br>Air Cat 6.8 4.9 74.5 13.7                                                        |
| 64       | 4.2                  | 9                         | 100                                | 100     | 90                         | 100     | 10                          | 0       | 78.1                               | 74.6    | 21.9                                | 25.4    | 0                                                                  | 13.7    |                                                                                                                       |
| 21       | 3.4                  | 11                        | 76                                 | 76      | 67                         | 73      | 11.9                        | 4.0     | 61.3                               | 40.0    | 19.4                                | 45.2    | 3.4                                                                | 25.9    | O <sub>2</sub> Cat 7.4 0.6 91.5 0.5<br>Air Cat 5.2 4.5 54.8 35.5                                                      |
| 16       | 3.8                  | 12                        | 150                                | 100     | 132                        | 87      | 12.0                        | 13      | ..                                 | 46.4    | ..                                  | 46.7    | ..                                                                 | 46.4    |                                                                                                                       |
| 66       | 3.5                  | 12                        | 75                                 | 75      | 70                         | 60      | 6.7                         | 20      | 59.5                               | 42.7    | 20.7                                | 44.1    | 3.1                                                                | 11.6    | Air Cat 4.0 0 53.3 42.7<br>O <sub>2</sub> Cat 8.6 1.8 85.0 4.4                                                        |
| 67       | 3.3                  | 12                        | 75                                 | 75      | 62                         | 50      | 17.4                        | 33.3    | ..                                 | 34.8    | ..                                  | 53.6    | ..                                                                 | 8.6     |                                                                                                                       |
| 12       | 2.0                  | 22                        | 100                                | 100     | 90                         | 86      | 10                          | 14      | ..                                 | ..      | ..                                  | ..      | ..                                                                 | ..      | Air Cat 6.3 3.2 71.2 18.8<br>O <sub>2</sub> Cat 4.9 8.4 69.5 17.2                                                     |
| 17       | 2.6                  | 23                        | 100                                | 75      | 84                         | 66      | 16                          | 11      | ..                                 | ..      | ..                                  | ..      | ..                                                                 | ..      |                                                                                                                       |
| 10       | 3.0                  | 27                        | 100                                | 100     | 76                         | 90      | 24                          | 10      | ..                                 | ..      | ..                                  | ..      | ..                                                                 | ..      |                                                                                                                       |

\*Approximately same weight for both cats in each experiment.

diffuses out of the intestine and stomach even more rapidly than when oxygen is breathed. It has been shown repeatedly (1), (2), and again in these experiments that once the intestine becomes inflated by any gas, nitrogen will diffuse into the intestine from the blood until the partial pressure in the blood and intestine is equalized at 4-5 of an atmosphere. In an animal breathing air the decrease in volume resulting from the escape of hydrogen into the blood is to a considerable extent nullified by the concomitant entrance of nitrogen from the blood into the gut in very considerable volume. The decompressing action of oxygen inhalations is not to be credited to any properties inherent in oxygen but to the fact that by shutting nitrogen out of the inspired air the direction of flow of nitrogen must be away from the intestine and toward the lung, thus preventing diffusion into the intestine. Pure oxygen may thus serve not only to facilitate the absorption of nitrogen already present in the gut but as a prophylactic against its accumulation secondary to the generation of other gases within the intestine.

From what has been said, it follows that the decrease in the total gas volume of the distended intestine will be directly dependent on the concentration of oxygen in the inspired air. The closer it is to 100% the better the effect. A few experiments with 70% oxygen failed to yield results comparable to those with higher percentages.

If the use of 100% oxygen for a period of not less than 12 hours is to be considered for clinical application for the relief of gaseous distention it is essential to inquire whether interruptions to continuous administration which feeding and nursing may demand would, by temporarily admitting nitrogen into the blood, substantially reduce the beneficial effects of the oxygen already inhaled. In six experiments (Table I) pure oxygen was given for four three-hour periods with intervals of air breathing varying from one-half to one hour. The residual gas volumes compared favorably with those obtained by continuous oxygen inhalation. The volume of nitrogen which may diffuse into the intestine during the air breathing interval is apparently insuff-

ficient to vitiate the decrease in volume effected by the oxygen already inhaled. Intermittent oxygen, allowing reasonable periods for rest, feeding or nursing, may therefore be expected to accomplish about the same results as continuous oxygen.

We have limited this study to the factors governing the diffusion of hydrogen and nitrogen because, as already stated, these are the gases of consequence in distention. Methane is the only other relatively non-absorbable gas which might occasionally become a factor in distention, i.e., when the gastro-intestinal tract happens to be loaded with foods rich in cellulose. Since this is an unlikely occurrence in distention as ordinarily encountered in post-operative patients or in most other types of distention in the sick, methane can for practical purposes be ignored.

In the treatment of distention the stomach, like the colon, can be readily decompressed because the gases are accessible by a rubber tube. Since the absorption of nitrogen and hydrogen from the stomach is not substantially improved by the inhalation of pure oxygen it follows that the use of this agent will not obviate the need of removing these gases from the stomach by the Levin tube or the Wangenstein gravity suction apparatus.

During the administration of pure oxygen\* nitrogen can no longer enter the gastro-intestinal tract from the blood or by mouth except when feeding or nursing is done during a respite in room air. As far as possible therefore these procedures would best be carried out while the patient is in the oxygen tent. The selection of foods should take account of the gas producing properties of the various types ordinarily given such patients (1). Certain carbohydrates and milk especially should be avoided.

Where it is of vital importance to keep the gastro-intestinal tract as collapsed as possible, e.g., in peritonitis, or in cases suspected of organic obstruction in whom surgery is being withheld, or in order to avoid tension on suture lines following gastro-intestinal

\*A tent suitable for this purpose has been devised for clinical use and will be described shortly elsewhere.

surgery, oxygen may prove to be a valuable adjunct to the usual measures.

### SUMMARY AND CONCLUSIONS

1. When the empty small intestine of the air breathing cat, ligated at the pylorus and ileocecal valve, is inflated with pure nitrogen, there is a slight increase in total gas volume at the end of six hours. During the succeeding 18 hours a decrease of about 16% in total gas volume occurs.

2. When oxygen is substituted for air as the respiratory gas in such animals there is a decrease of 26% in the total gas volume of the small intestine after six hours. The reduction in distending volume continues progressively until about 61% of the total gas volume has been absorbed within 18 to 24 hours.

3. Pure oxygen given intermittently for 12 hours is approximately as effective as when given continuously. The free intervals may last one hour, possibly longer, without destroying the effect obtained by the oxygen already inhaled.

4. When the stomach of a cat breathing oxygen is distended with nitrogen, the total gas volume is, as a rule about as great after periods varying from 6-24

hours as at the beginning of the experiment. When the stomach of a cat breathing oxygen is distended with hydrogen, the total gas volume is reduced some 10% after 12-24 hours. The inhalation of pure oxygen therefore cannot be expected to deflate a stomach distended by nitrogen or hydrogen.

5. The difference in the effect of oxygen on the total gas volume between the stomach and small intestine inflated with nitrogen is probably due to the difference in the surface area available for gaseous exchange.

6. Hydrogen is much more readily absorbed from the gastro-intestinal tract than nitrogen. Pure oxygen inhalation does not increase the rate of absorption of hydrogen. Nevertheless by preventing the access of nitrogen to the intestine oxygen causes a greater decrease in the total gas volume than occurs when air is breathed.

7. The efficacy of oxygen for the absorption of gases from the small intestine is directly proportional to the concentration of oxygen.

8. The clinical implications of the foregoing observations are discussed.

### REFERENCES

1. Fine, J., and Levenson, W. S.: Effect of Foods on Postoperative Distention. *Am. Jour. Surg.*, 12:184, 1933.
2. McIver, M. A., Redfield, A. C., and Benedict, E. B.: Gaseous Exchange Between Blood and Lumen of Stomach and Intestines. *Am. Jour. Phys.*, 76: 92, 1926.
3. Shaw, L. A. and Behnke, A. R.: Personal communication.
4. Custor, J.: Ueber die Relative Grosse des Darmkanales und der Hauptsachlichsten Körpersysteme bei Menschen und bei Wirbelthieren. *Arch. fur Anat. und Phys.*, 1873, p. 478.
5. Sappey, V.: *Traite d'Anatomie, Descriptive*, Vol. IV, 1874.
6. Dargein, P.: Surface et Volume Compare de L'Estomac et du Duodenum. *Bibliographie Anatomique*, 7:207, 1899.

## ABSTRACTS

SAMUEL MORRISON, M.D., AND MAURICE FELDMAN, M.D.

*The Effect of Bacteria on the Normal Stomach and on Acute Experimental Gastric Ulcer in Dogs. Am. Jour. Med. Sciences, May, 1935, p. 696.*

In a previous study it was determined that ulcers could be produced by the injection of 1% hydrochloric acid solution into the gastric tissue and that such ulcers have a tendency to heal usually within a period of three weeks. Chronic ulcers did not occur from this procedure alone, so the question of infection was studied by bringing the gastric mucosa and the acute ulcer into intimate contact with potent cultures of the common organisms.

Regarding the effect of gastric secretion upon bacteria, Bartle and Hawkins found no germicidal effect was demonstrable with free HCl concentrations below 0.04%; but gastric juice containing 0.08% and upward was bactericidal.

In their experiments the authors administered the bacteria mixed with food so as to dilute and neutralize the gastric contents and insure the retention of the bacteria in the stomach for longer periods and protect them from "acid" attack by their admixture with the food. Bacteria alone were given in one group of dogs, and in another group large amounts of sodium bicarbonate were administered to neutralize the gastric acidity while the bacteria were in the stomach.

In other experiments ulcerations were produced by injection of hydrochloric acid into the gastric wall and the animals fed bacteria alone and with the addition of sodium bicarbonate.

The bacteria exhibited were: *Streptococcus* 1.5 billion per cc.; *B. Coli* and *staphylococcus* 5 billion per cc.; the site of injection being marked with a bead. In Table 1 it is shown that in all the dogs injected variously with *staph. aureus*, *S. Viridans* and *B. Coli*, the mucosa at

autopsy was found normal. In these dogs no gastric ulcers had first been produced by injecting the gastric wall first with 1% hydrochloric acid.

In Table 2, is portrayed the effect of daily feeding of the above bacteria after HCl injection. Eight dogs were fed *staph. aureus*, 4 dogs were fed *S. Viridans* and 7 dogs were fed *B. Coli*. To three dogs no sodium bicarbonate was fed and at autopsy definitely healed ulcers were found. In 5 dogs one ounce of sodium bicarbonate was fed and at autopsy, one deep ulcer, one perforating ulcer, one definite ulcer and one completely healed ulcer were found. In the *S. Viridans* dogs no sodium bicarbonate was given and at autopsy no ulcer was found. Two dogs were given an ounce of sodium bicarbonate daily and in these definite healing ulcers were found. Of the *B. Coli* dogs no sodium bicarbonate was fed in three and at autopsy 2 showed healed ulcers and one a normal mucosa. In 4 *B. Coli* dogs one ounce of sodium bicarbonate was fed daily for from 3 to 27 days and two perforated ulcers were found at autopsy; one dog showed a small ulcer and one had no ulcer. Time in days in all these experiments for both tables were variously from 3 to 57.

As a separate study 3 dogs were injected with 0.5 cc. of 1% hydrochloric acid into the muscular walls of the stomach. Necrotic ulcers were produced in three days and then 1 cc. of *S. Viridans* (24 hour broth culture) was injected through the serosa into the muscular and sub-mucosal areas surrounding the ulcers.

Soda Controls. In 2 dogs in which ulcers were produced soda alone was given for 88 days; both revealed healed ulcers.

In the summary it is stated that "chronic gastric ulceration cannot be produced by bacteria acting on acute hydrochloric acid ulcers, at least not in the dog. It seems that another factor must play an important role in its chronicity."

Allen Jones, Buffalo.

## SECTION III—Nutrition

### The Role of Serum-Calcium Fractions in the Effect of Viosterol on the Bleeding Tendency in Jaundice\*

By

J. S. GRAY, M.S.

and

A. C. IVY, Ph.D., M.D.

CHICAGO, ILLINOIS

McNEALY, Shapiro and Melnick (1) have reported that viosterol in therapeutic doses is useful in controlling the hemorrhagic diathesis which frequently complicates jaundice. Since calcium therapy has been widely used in the treatment of this bleeding tendency, and since viosterol is known to play an important rôle in calcium metabolism, it was thought desirable to determine the effect of the viosterol administered to these patients on both total and diffusible serum calcium.

#### METHODS

Fifty-six of the jaundiced patients studied by McNealy, Shapiro and Melnick (1) at Cook County Hospital, Chicago, constituted the subjects for this work. Viosterol 250 D was administered, 30 gtts. t.i.d. *In those cases with acholic stools, bile salts were given to insure proper absorption of the vitamin.* An initial blood sample was taken and then viosterol therapy was instituted, blood samples being taken each week thereafter until the case was concluded, usually within two to three weeks. A control group consisted of patients given no viosterol, but in all other respects receiving identical treatment. In no case was calcium administered.

Twenty c.c. blood samples were taken, (usually in the early morning), with a clean, dry syringe and without hemolysis. At the same time the bleeding-time was obtained by the venostasis method (2). The blood samples were brought to the laboratory and the calcium analyses begun the same day. All icteric indices were determined at the hospital. Diffusible calcium analyses were not begun until the work had been some time in progress. The data presented are from completed patient-records only.

For the determination of the ultrafiltrable calcium, the high pressure ultrafiltration method described by Nicholas (3) was employed. Ultrafiltration was carried out at 150 lbs. pressure of nitrogen gas. Nicholas (3) showed that variations in pressure from 50 to 200 lbs. had no effect on the concentration of calcium in the ultrafiltrate. Hertz (4) denies that pressure influences the diffusible calcium and Cox and Hyde (5) present evidence that variations in pressure are without effect when the membrane, as in this apparatus, is well supported, rather than suspended as a sac. Table I shows that methods employing higher pres-

ures<sup>†</sup> do not necessarily give higher yields of diffusible calcium.

The Nicholas method has the advantages of speed of filtration and of uniformity of the membrane employed. Du Pont cellophane No. 300 is used as an ultrafiltration membrane.

Nicholas (3) reported that cellophane is impermeable to serum proteins, uniform in permeability to calcium, and that successive sample of ultrafiltrate from the same process of ultrafiltration contain the same concentration of calcium. Similar tests were made in this laboratory, confirming these results. Further, the membrane is impermeable to bilirubin.

From 4 to 5 c.c.'s of serum were ultrafiltered, the calcium being determined in 2 c.c. quantities of ultrafiltrate by the Clark-Collip method (6). Ordinarily about 4 hrs. were required to obtain 2 c.c. of ultrafiltrate. During this time evaporation was prevented by maintaining the receiving tube snugly against the ultrafilter. The non-diffusible calcium was obtained by difference (total serum Ca minus Ca in ultrafiltrate), no correction being made for the absence of protein in the ultrafiltrate. This method for the determination of diffusible calcium is much superior to previous collodion membrane methods in regard to simplicity of operation, and probably also in consistency of results obtained in the hands of persons not skilled in making collodion membranes.

#### RESULTS

*Normal Students:* The diffusible serum calcium of 13 healthy medical students was determined. These normal values ranged from 1.5 mg. to 6.5 mg., averaging 5.8 mg. Expressed as the percent of total calcium the range is from 46% to 58%, averaging 54%. This is in contrast to the 64% average reported by Nicholas (3). The procedure and apparatus used in this work were identical with those employed by Nicholas. A possible explanation of the difference lies in the fact that Nicholas subjects were Texans, presumably exposed the year round to the sun's rays, whereas our subjects were laboratory workers in Chicago, who were exposed very little to the sun's rays. Ultraviolet irradiation *in vitro* has been reported by Clark (7) to increase the diffusible calcium of serum, although Moritz (8) was unsuccessful in his attempts to in-

\*From the Department of Physiology and Pharmacology, Northwestern University Medical School, Chicago, Illinois. This work was aided in part by a grant in aid from the Mead-Johnson Company.

Submitted May 24, 1935.



## 3-a

TABLE I

## Normal Diffusible Calcium of Serum (Human)

| Date | Observer                 | Diffusible Calcium Mg. |      | Diffusible Calcium % |                          | Pressure  | Method                             |
|------|--------------------------|------------------------|------|----------------------|--------------------------|-----------|------------------------------------|
|      |                          | Range                  | Ave. | Range                | Ave.                     |           |                                    |
| 1921 | Meysenbug et al (59)     | 6.4-7.9                | 7.1  | 65-73                | 66                       | 0         | Collodion compensation di-lysis    |
| 1924 | Hirth, Tschimber (51)    | ....                   | ..   | 50-60                | 55                       | 150 mm Hg | Collod. impregnated Bachold filter |
| 1926 | Updegraff et al (52)     | 3.6-4.6                | 4.1  | 39-62                | 46                       | 150 mm Hg | Collod. ultrafiltration-dialysis   |
| 1926 | Kirk & King (23)         | 5.2-7.5                | 5.9  | 67-81                | 59*                      | 150 mm Hg | Collod. sac ultrafiltration        |
| 1927 | Liu (33)                 | 4.5-5.8                | 5.0  | 43-58                | 51                       | 150 mm Hg | Updegraff et al                    |
| 1928 | Bokelmann & Bock (58)    | 5.0-6.5                | 5.6  | 50-66                | 55                       | 0         | Commensation dialysis              |
| 1929 | Hertz (4)                | 4.4-4.9                | 4.7  | 46-52                | 48                       | 160 lb.   | Commercial pressure filter         |
| 1930 | Snell & Greene (14)      | 4.5-5.5                | 5.2  | 45-60                | 52                       | 150 mm Hg | Updegraff et al                    |
| 1930 | Brown & Greenbaum (56)   | 4.8-6.0                | 5.4  | 48-55                | 52                       | 150 mm Hg | Updegraff et al                    |
| 1931 | Spiegler (55)            | ....                   | 4.3  | ....                 | 49                       | 14 lb.    | Collodion impregnated filter       |
| 1932 | Scholtz (57)             | 6.3-7.0                | 6.7  | 59-64                | 62                       | 37 lb.    | Commercial ultrafilter             |
| 1930 | Greenberg & Gunther (16) | 4.2-6.8                | 5.0  | 45-55                | 50                       | 150 mm Hg | Collodion sac ultrafiltration      |
| 1930 | Ray & Photnk (163)       | 4.4-6.0                | 5.3  | 40-59                | 47                       | 150 mm    | Greenberg & Gunther                |
| 1932 | Watehorn & McCahee (60)  | 4.8-5.8                | 5.2  | 45-60                | 51                       | 150 mm Hg | Greenberg & Gunther                |
| 1932 | Weill (50)               | ..                     | ..   | 50-60                | 55                       | 25 lb.    | Collodion ultrafilter              |
| 1932 | Nicholas (3)             | 6.0-8.3                | 7.2  | 60-67                | 64                       | 150 lb.   | Cellophane ultrafiltration         |
| 1933 | Benjamin & Hess (34)     | ...                    | 5.7  | ...                  | 52                       | 150 mm Hg | Greenberg & Gunther                |
| 1933 | Bendien & Snaper (53)    | 4.6-6.1                | 5.2  | 45-57                | 50                       | 100 mm    | Collodion sac ultrafiltration      |
| 1933 | Needels & Marberg (54)   | ....                   | 5.8  | ....                 | 54                       | 150 mm    | Greenberg & Gunther                |
| 1933 | Freeman & Farmer (31)    | ..                     | ..   | ....                 | 65                       | 150 mm    | Greenberg & Gunther                |
| 1933 | Searle & Michaels (38)   | 3.9-6.2                | 5.0  | 40-61                | 50                       | 150 mm    | Greenberg & Gunther                |
|      |                          | Average                |      | ..                   | 54.0% Diffusible Calcium |           |                                    |
| 1935 | Gray & Ivy               | 5.1-6.5                | 5.8  | 46-59                | 54                       | 150 lb.   | Nichols' Method                    |

\*Corrected for Obviously low total calciums averaging 8 mg./100 cc.

crease the diffusible calcium of rabbits by irradiating the animals.

That this high pressure ultrafiltration method gives a true value for diffusible serum calcium is suggested by an analysis of previous reports of normal values in man. The literature contains 21 reports (Table I) of the diffusible calcium of normal human subjects. They vary widely from 46% to 66%, depending upon the method used. The average of all the reported values is 54.0% which compares favorably with the 54% average which we have obtained. Additional support is found in the calcium content of the cerebrospinal fluid, which has been considered a dialysate of the blood, at least under normal conditions (9) (10) (11) (12) (13) (4) (37) (38). The average of 13 reports on the cerebrospinal fluid calcium in normal humans is 50.7% (Table II). It is significant that the averages of many analyses by different investigators employing different methods give results which compare with those obtained by us using the Nicholas method.

**Jaundiced Patients:** In jaundice the total serum calcium was found to be within normal limits, although the average is slightly lower than that of the normal group (Table III). Similar data have been reported by a number of other observers (14) (15) (16) (17) (18) (19) (20) (21) (40). The average ultrafilterable calcium was also normal in the jaundice cases, although a greater range of variation was noted when compared with those in the normal series. There was no correlation between the factors of bleeding-time, icteric index, and diffusible calcium, thus confirming the work of other investigators (14) (19) (16) (4) (40) (53). Emerson (22) and Kirk and King (23), however, report a decrease in diffusible calcium in jaundice.

Viosterol administered to the patients with a prolonged "venostasis-bleeding time" uniformly reduced it to within normal limits (240 secs.). The effect of viosterol on the total serum calcium (Table V) was limited to a prevention of the slight fall that would have occurred had they received no viosterol, as evi-

## 3-b

TABLE II

## Normal Cerebrospinal Fluid Calcium (Human)

| Observer                 | Date | Cerebrospinal Fluid In Milligrams |      | Calcium as % of Serum Calcium |       |
|--------------------------|------|-----------------------------------|------|-------------------------------|-------|
|                          |      | Range                             | Ave. | Range                         | Ave.  |
| Kummer, Minkoff (45)     | 1921 | 5.0-5.2                           | 5.1  |                               | 51*   |
| Leicher (46)             | 1922 | 4.7-5.3                           | 5.1  | 43-48                         | 45    |
| Pineus, Kramer (45)      | 1923 | 4.4-5.0                           | 4.8  | 42-48                         | 46    |
| Neustädter et al (42)    | 1925 | 4.6-7.8                           | 5.8  |                               | 58*   |
| Nourse et al (44)        | 1925 | 4.3-5.3                           | 4.8  | 47-53                         | 49    |
| Liehrnit (43)            | 1926 | 5.2-6.5                           | 6.0  | 50-68                         | 60    |
| Eisler (41)              | 1928 | 4.9-5.6                           | 5.2  |                               | 52*   |
| Cantarrow (37)           | 1929 | 4.5-5.5                           | 5.0  | 45-55                         | 50    |
| Morgulis, Perley (40)    | 1930 | 4.8-5.0                           |      | 46-51                         | 49    |
| Merritt, Bauer (39)      | 1931 | 4.5-5.2                           | 5.0  | 45-53                         | 50    |
| Fremont-Smith et al (48) | 1931 | 4.1-5.4                           | 4.7  | 46-54                         | 50    |
| Gerney, Lespagnol (47)   | 1931 | 5.8-6.8                           | 6.4  | 48-56                         | 51    |
| Searle, Michaels (38)    | 1933 | 4.4-5.4                           | 4.8  | 43-56                         | 48    |
| Average                  |      |                                   |      |                               | 50.7% |

\*Total serum calciums not given: assumed to be 10 mg.

5-a

TABLE III  
Diffusible Calcium in Jaundice

| No. Patient's | Diagnosis                     | Icteric Index | Total Calcium | Non-Diff. Calcium | Diffusible Calcium | % Diffusible Calcium | Ivy Bleeding Time in Seconds |
|---------------|-------------------------------|---------------|---------------|-------------------|--------------------|----------------------|------------------------------|
| 13            | Normal                        | Normal        | 10.7          | 4.9               | 5.8                | 54                   | Normal*                      |
| 7             | C. B. Dust Stone              | 55            | 10.3          | 5.1               | 5.2                | 50                   | 340                          |
| 6             | Carcinoma                     | 66            | 9.6           | 4.4               | 5.2                | 54                   | 510                          |
| 3             | Cirrhosis                     | 52            | 9.1           | 4.1               | 5.0                | 55                   | 470                          |
| 1             | Cholangitis                   | 31            | 9.8           | 4.8               | 5.0                | 51                   | 340                          |
| 1             | Toxic Hepatitis               |               | 11.2          | 4.6               | 6.6                | 59                   | 650                          |
| 1             | Thrombo. Purpura              | Normal        | 9.5           | 4.7               | 4.8                | 51                   | 670                          |
| 1             | Catarrhal Jaundice            | 54            | 9.5           | 3.2               | 6.3                | 66                   | 80                           |
| 1             | Cholecystitis                 | Normal        | 10.8          | 5.1               | 5.7                | 53                   | 320                          |
|               | Jaundice Cases Post-operative | ..            | 9.4           | 4.4               | 5.0                | 53                   | 140                          |

\*Less than 240 seconds.

denced by the fall in total serum calcium in the control group (Tables III, IV and V).

Reports in the literature are conflicting as to the ability of *therapeutic doses* of irradiated ergosterol to raise the serum calcium level (24) (25) (26) (27) (28) (29). Therapeutic doses of viosterol did not raise the total serum calcium in our jaundiced patients. Jaundiced patients also show a resistance to the hypercalcemic effect of intravenous calcium, according to Walters and Bowler (30).

Neither is the literature in agreement as to the effect of viosterol on the diffusible calcium (31) (32) (33) (34) (35) (36). The diffusible serum calcium values showed a slight decrease under the influence of viosterol. Unfortunately, just those subjects who showed a fall in total calcium happened to have the diffusible fraction determined, so that no particular significance is attached to the fall in percentage of diffusible calcium. *However, these results suggest that jaundiced patients should receive calcium in addition to viosterol.*

*From our results the explanation of the effect of viosterol in reducing the bleeding time in jaundice is not to be found in its effect on blood calcium, or its ultrafilterable fraction.*

### DISCUSSION

Although a "calcium deficiency" undoubtedly exists in jaundice, (30) (61) (62) (63) (64) (65) (66), the chemical evidence indicates *either* that it is not of sufficient degree to be reflected in the serum calcium, either total or diffusible (14) (19) (16) (4) (40) (53) (15) (17) (18) (20) (21), or our present methods are not sufficiently adequate to demonstrate the change in the blood. The chemical evidence, however, is corroborated by the physiological, for the absence of neuromuscular hyperirritability in jaundice indicates a physiologically adequate calcium content of the blood. Furthermore, a calcium deficiency would be expected to hasten the appearance and increase the severity of tetany in a parathyroid-ectomized jaundiced animal,

whereas in reality it has the reverse effect (64) (67). Of course, it may be argued that the state of jaundice has a depressing action which counteracts a chemically "masked" calcium deficiency. Nevertheless, the facts afford definite proof that *bilirubin does not combine with the calcium ion of the blood to produce a functional deficiency* of the latter sufficient to decrease the coagulability of the blood, as has been the suggested explanation for the bleeding encountered in icteric patients (65) (18) (68) (76). If more proof be necessary, it might be pointed out that the bleeding tendency bears no relation to the intensity of the icterus (14) (69) (70) (16) (88), nor is bleeding found in *icterus neonatorum* (164). A search of the literature failed to reveal such a tendency in congenital hemolytic jaundice.

Granted a "masked", functional, serum calcium deficiency, it must still be shown how such a condition could be responsible for a hemorrhagic tendency. Tetany, the example of serum calcium deficiency, *par excellence*, is unassociated with a tendency to bleed (71) (72) (73). Furthermore, it has been reported (74) (75) that citrates and oxalates delay coagulation, not so much by removing calcium as by combining with fibrinogen to render the latter incoagulable.

It has even been proposed that it is the non-diffusible calcium which figures in blood coagulation (77) (78) (79), but this fraction, also, remains unaltered in jaundice. This fraction is low in nephrosis (33) and in parathyroid deficiency (4) (12) (33) (157) (158) (159) (160) (161) (162), but neither the former (165) nor the latter disease (71) (72) (73) is associated with a bleeding tendency. Furthermore, the nondiffusible calcium is bound to serum proteins (33) (52) (80) (81) (82) (83) (84) (85) (86) (87), and probably to the albumin fraction only (53).

Finally, it must be borne in mind that the calcium deficiency explanation of icteric bleeding is based on the fact that agents which precipitate calcium delay or prevent coagulation, a mechanism which cannot be

TABLE IV  
Effect of Viosterol on Diffusible Calcium in Jaundice

| Treatment        | No. Cases | Time             | Total Calcium | Non-Diff. Calcium | Diffusible Calcium | % Diffusible Calcium | Ivy Bleeding Time |
|------------------|-----------|------------------|---------------|-------------------|--------------------|----------------------|-------------------|
| Viosterol        | 5         | Initial analysis | 10.1          | 5.2               | 4.9                | 49                   | 410               |
| (30 gts. t.i.d.) |           | 1-2 wks. later   | 9.3           | 5.1               | 4.3                | 46                   | 270               |
| Control          | 3         | Initial analysis | 10.1          | 3.7               | 6.4                | 63                   | 450               |
| (No Viosterol)   |           | 1-2 wks. later   | 10.1          | 4.9               | 5.2                | 52                   | 430               |

reconciled with the fact that a delayed coagulation-time is not a uniformly characteristic finding even in the bleeding jaundiced patient (69) (70) (89) (90) (2) (100) (105) (19). *In the light of our present knowledge, therefore, a disturbance of calcium metabolism per se offers no explanation for the hemorrhagic diathesis of jaundice.*

Bile salts *in vitro* are known to prolong the clotting-time of blood (150), and *in vivo* to delay the formation of experimental thrombi (91). In jaundice undoubtedly they are present in abnormal amounts (142) (99) (97) (98), consequently bile salts have not been overlooked in the search for the etiological agents of this bleeding tendency. However, they reach their highest level in the blood and urine early in the course of the disease, (92) (93) (94) (95) (96), for the "back pressure" of the bile in obstructive jaundice damages the liver (109) (110) (111) (112) (101) (21) (94) (102) sufficiently to inhibit the formation of bile salts (97) (98) (95) (94) (169) (170) (171) (172) (173) (174) (175), and hence they are at their lowest concentration late in jaundice when hemorrhage is most frequently encountered (103) (89) (104) (88). No correlation has been found between the "Pettenkoffer substances" of the blood and the bleeding tendency (99). Since bile salts are rapidly eliminated from the blood stream, after removal of the obstruction, probably they are absent during the bleeding which complicates post-operative recovery (94).

The concentration of bile necessary to prolong the coagulation-time of the blood *in vitro* is far in excess of the amounts found in the blood in jaundice (106) (104), although this may not be true of the intravenous injection of bile salts (91). Attempts to reproduce the hemorrhagic tendency experimentally by a successful anastomosis of the common bile duct to the *vena cava* have been fruitless (107). The effect on the capillary walls of abnormal amounts of bile in the blood over a long period of time has never been investigated. However, as far as it is known at present, the hemorrhagic tendency in jaundice is not attributable to the presence of bile salts in the blood.

Frequently it has been observed that the bleeding tendency parallels the extent of liver damage (100) (103) (107) (108) (89) (1) (70). Obstruction of the bile passages is known to produce liver damage. The greater the duration of the obstruction, the more extensive becomes the hepatic involvement, and it is in just such long-standing cases that hemorrhage is most to be feared. Frequently it has been observed clinically that hemorrhage is most serious in cases of malignant obstruction (114) (115) (116), and in such cases the liver is usually markedly affected (107). Bleeding often manifests itself shortly after operation at a time when anesthesia and operative trauma have contributed to the hepatic injury. Since recovery of the damaged liver after obstruction requires time (166) (167) (168), it may be still incomplete a week after obstruction, when the danger of hemorrhage still is present (89) (104) (117).

The liver, undoubtedly, plays an important rôle in blood coagulation. It is believed to be the site of formation of fibrinogen (113 and antiprotease (118). All types of injury, such as phosphorus carbon tetrachloride (121) (119), and chloroform (120) poisoning, interference with hepatic circulation (122), acute yellow atrophy (123) and hepatectomy itself (124) produce alterations in blood coagulability. At present

5-b

TABLE V

*Effect of Treatment on Total Calcium in Jaundice*

| Treatment              | No. of Cases | Before        |                   | After         |                   |
|------------------------|--------------|---------------|-------------------|---------------|-------------------|
|                        |              | Total Calcium | Ivy Bleeding Time | Total Calcium | Ivy Bleeding Time |
| None (Controls)        | 9            | 9.9           | 400               | 9.5           | 499               |
| Viosterol              | 16           | 9.7           | 410               | 9.7           | 220               |
| Operation No Viosterol | 5            | 10.2          | 290               | 9.4           | 140               |

one can only speculate as to the exact mechanism by which liver damage in jaundice might lead to a hemorrhagic diathesis. It is certainly not through alteration in blood fibrinogen (105) (88) (19) (125). Some investigators believe that the liver injury results in an excess of antiprotease in the blood which is responsible for the hemorrhage (108) (100) (126) (127) (128). Antiprotease, or "heparin", increases the sedimentation rate of erythrocytes (129), which has been used empirically with some success as an indication of a bleeding tendency in jaundice (90) (69) (130) (131). But, there is as yet no direct, quantitative proof or agreement in regard to the presence of excessive amounts of "heparin" in jaundiced blood.

Some recent work indicates that in jaundice the bleeding tendency and the fragile clot are due to the presence of abnormal amounts of cysteine in the blood (19). Practically nothing is known about the amount of cysteine in the blood under normal or pathological conditions, and very little concerning its metabolism, so that more investigation is necessary for a proper evaluation of this factor.

If it be admitted that liver involvement fundamentally is related to the bleeding tendency, then a possible explanation is provided for the beneficial effects reported with the use of calcium (132) and glucose (133) (149) in the control of hemorrhage in jaundice. Glucose has long been known to exert a "protective" action on the liver (133) (134) (135) (136) (137) (138) (139) (140) (141). Calcium has been shown to counteract certain poisons which, selectively, affect the liver (121) (143) (144) (145) (156). It has been used clinically in eclampsia and acute liver injury (146) (147) and to prevent complications resulting from arsenic therapy (148) with reported excellent success. There is very little evidence for such action on the part of viosterol, although it has been reported to reverse the frequently positive hemoclastic crises observed in dementia praecox (133). Viosterol has been shown, however, to decrease the coagulation-time in normal rats through increasing the thrombocyte count (154) (155).

The venostasis method of obtaining the bleeding-time involves the production of a condition of venostasis in the area where the bleeding is experimentally induced. It is significant that a latent tendency to hemorrhage can be revealed frequently only by subjecting the incised vessels to this additional stress (2). Contractility and retractility of the capillaries, and thrombus formation in the vessels and tissues constitute the chief mechanism for accomplishing hemostasis (151) (152). Since the coagulation-time may be normal in icteric bleeding, an exaggerated venostasis bleeding-time must reveal either a fragility of the clot or a deficiency in capillary contractility, or both, which, on the basis of the available evidence, is sec-

ondarily due to hepatic injury rather than to serum calcium changes or circulating bile salts.

## CONCLUSIONS

1. Total serum calcium and ultrafilterable serum calcium were found to lie within normal limits in jaundice.
2. No correlation was found between the ultrafil-

terable calcium, the "venostasis bleeding time", or the icteric index.

3. Viosterol, which restores the normal bleeding time in jaundice, unless the liver damage be extreme, does not do so by altering the serum calcium, either total or ultrafilterable.

4. The etiology of the hemorrhagic diathesis in jaundice is discussed.

## REFERENCES

1. McNealy, Shapiro, Melnick: *S. G. O.*, 60:785, 1935.
2. Ivy, Shapiro, Melnick: *S. G. O.*, 60, 781, 1935.
3. Nicholas: *J. B. C.*, 97:457, 1932.
4. Hertz: *Z. F. Kinderheil.*, 47:215, 1929.
5. Cox, Hyde: *Am. J. Hyg.*, 16:567, 1932.
6. Clark, Collip: *J. Bio. Chem.*, 63:461, 1925.
7. Clark: *Am. J. Hyg.*, 3:481, 1923.
8. Moritz: *J. Biol. Chem.*, 64:81, 1925.
9. Stary, Kral, Winternitz: *Z. f. d. ges. exp. Med.*, 66:671, 1929.
10. Greenberg: *Proc. Soc.*, 27:514, 1929-30.
11. McCance, Whitehorn: *Quart. J. Med.*, 24:371, 1930-31.
12. Herbert: *Biochem. J.*, 27:1978, 1933.
13. Katzenbach: *J. Pharm. Exp. Therap.*, 51:436, 1934.
14. Snell, Greene: *Am. J. Physiol.*, 92:630, 1930.
15. Linton: *Ann. Surg.*, 93:707, 1931.
16. Greenberg, Gunther: *Arch. Int. Med.*, 45:953, 1930.
17. Koechig: *J. Lab. Clin. Med.*, 9:679, 1923-24.
18. Cantarow, Dodek, Gordon: *Arch. Int. Med.*, 40:129, 1927.
19. Carr & Foote: *Arch. Surg.*, 29:277, 1934.
20. Zimmerman: *Am. J. Med. Sci.*, 174:379, 1927.
21. Snell, Greene, Rowntree: *Arch. Int. Med.*, 36:273, 1925.
22. Emerson: *J. Lab. Clin. Med.*, 14:122, 1928-29.
23. Kling: *J. Lab. Clin. Med.*, 11:928, 1925-26.
24. Kretz: *Klin. Woch.*, 6:1171, 1927.
25. Grimm: *Am. Rev. Tuberculosis*, 23:576, 1931.
26. Hess, Lewis: *J. A. M. A.*, 91:783, 1928.
27. Kaminsky, Davidson: *Am. Rev. Tuberculosis*, 22:48, 1930.
28. Losch: *Klin. Woch.*, 7:2148, 1928.
29. Bauer, Marble, Chaffin: *J. Clin. Inv.*, 11:1, 1932.
30. Walters, Bowler: *S. G. O.*, 39:200, 1934.
31. Freeman, Farmer: *Proc. Soc.*, 27:570, 1930.
32. Benjamin, Hess: *J. Bio. Chem.*, 103:629, 1933.
33. Liu: *Chin. J. Physiol.*, 1:331, 1927.
34. Benjamin, Hess: *J. Bio. Chem.*, 100:227, 1933.
35. Rodecort: *Z. f. Geburt. u. Gynäk.*, 94:784, 1929.
36. Timpe: *Arch. f. Gynäk.*, 146:240, 1931.
37. Cantarow: *Arch. Int. Med.*, 41:670, 1929.
38. Senile, Michaels: *Am. J. Physiol.*, 103:445, 1933.
39. Merritt & Bauer: *J. Bio. Chem.*, 90:216, 1931.
40. Morgulis, Perley: *J. Bio. Chem.*, 88:169, 1930.
41. Eiler: *Z. f. d. ges. exp. Med.*, 61:549, 1928.
42. Neustädter, Hala, Tolstouchow: *J. A. M. A.*, 85, 346, 1925.
43. Lefkint: *Klin. Woch.*, 5:556, 1926.
44. Nourse, Smith, Hartman: *Am. J. Dis. Child.*, 30:210, 1925.
45. Kummer, Melnikoff: *C. R. Soc. Biol.*, 85, 864, 1921.
46. Leicher: *Deut. Arch. f. Klin. Med.*, 141:196, 1922.
47. Gernsey, Lepassand: *C. R. Soc. Biol.*, 108, 1260, 1931.
48. Frenoy-Smith, Dailey, Merritt, Carroll, Thomas: *Arch. Neur. & Psychiat.*, 25:1271, 1931.
49. Pincus, Kramer: *J. Biol. Chem.*, 57, 463, 1923.
50. Weill: *C. R. Soc. Biol.*, 109, 925, 1932.
51. Hirth, Tschimber: *C. R. Soc. Biol.*, 91:592, 1924.
52. Underaaf, Greenberg, Clark: *J. Bio. Chem.*, 71, 87, 1926-27.
53. Hordien, Snapper: *Biochem. Z.*, 260, 105, 1933.
54. Needels, Marberg: *J. Lab. Clin. Med.*, 18, 1227, 1932-33.
55. Spiezler: *Arch. f. Gynäk.*, 145, 423, 1931.
56. Brown, Greenbaum: *Brit. J. Dermatol.*, 42:183, 1930.
57. Scholtz: *Deut. Arch. f. Klin. Med.*, 172, 472, 1932.
58. Bokelmann & Beck: *Arch. f. Gynäk.*, 133:305, 1928.
59. Meyenburg, Pappenheimer, Zucker, Murray: *J. Bio. Chem.*, 47:529, 1921.
60. Whitehorn, McCance: *Biochem. J.*, 26, 54, 1932.
61. Duttman: *Brüss. Beiter.*, 39:720, 1927.
62. Seidel: *Munch. Med. Woch.*, 2:7034, 1910.
63. McCrudden: *Endocrin. & Metab.*, 4:761, 1922.
64. Buchbinder, Kern: *Arch. Int. Med.*, 11:754, 1925.
65. King, Biechow, Pearce: *J. Exp. Med.*, 14, 159, 1911.
66. Buchbinder, Kern: *Am. J. Physiol.*, 80, 273, 1927.
67. Braucher: *Am. J. Physiol.*, 86, 39, 1928.
68. King, Stewart: *J. Exp. Med.*, 11, 673, 1909.
69. Linton: *Ann. Surg.*, 91, 694, 1930.
70. Storz, Schlangbaum: *Klin. Woch.*, 12, 184, 1933.
71. Kattman and Lidsky: *Z. f. Klin. Med.*, 71, 344, 1910.
72. Simpson, Basmussen: *Quart. J. Exp. Physiol.*, 10, 145, 1916.
73. Braucher: *Am. J. Physiol.*, 87, 221, 1928-29.
74. Stuber, Sano: *Biochem. Z.*, 134, 260, 1923.
75. Stuber and Focke: *Biochem. Z.*, 154, 77, 1924.
76. Haden: *Ohio State Med. J.*, 29, 487, 1933.
77. Vines: *J. Physiol.*, 55, 85, 1921.
78. Vines: *J. Physiol.*, 55, 287, 1921.
79. Stewart and Percival: *Biochem. J.*, 22, 558, 1928.
80. Ingraham, Lombard, Vischer: *J. Gen. Physiol.*, 16, 637, 1922-33.
81. Leck: *J. Gen. Physiol.*, 8, 451, 1926-27.
82. Greenberg, Gunther: *J. Bio. Chem.*, 85, 491, 1929-30.
83. Leck, Nichols: *J. Bio. Chem.*, 72, 6-7, 1927.
84. Spiezler: *Biochem. Z.*, 239:253, 1930.
85. Cushing: *J. Physiol.*, 53, 391, 1920.
86. Green, Power: *J. Bio. Chem.*, 91, 183, 1931.
87. Stear, Officer: *J. Bio. Chem.*, 91, 291, 1931.
88. Burke, Weir: *J. Lab. Clin. Med.*, 18, 657, 1932-33.
89. Wangenstein: *Ann. Surg.*, 88, 845, 1928.
90. Clute, Veal: *Surg. Clin. No. Am.*, 12, 593, 1932.
91. Johnson, Shionnyn, Rowntree: *J. Exp. Med.*, 48, 871, 1928.
92. Katayama: *Ann. Int. Med.*, 42, 916, 1928.
93. Fuentes, Apolo, Escules: *Z. f. d. ges. exp. Med.*, 73, 412, 1930.
94. Snell, Greene, Rowntree: *Arch. Int. Med.*, 40, 471, 1927.
95. Brakefield, Schmidt: *J. Bio. Chem.*, 67, 523, 1926.
96. Shattuck, Katayama, Killian: *Am. J. Med. Sci.*, 176, 103, 1928.
97. Rosenthal, Wilekeli: *Klin. Woch.*, 6, 781, 1927.
98. Chabrol, Bernard, Bariety: *Pres. Med.*, 36:849, 1928.
99. Rowntree, Greene, Aldrich: *J. Clin. Inv.*, 4, 545, 1927.
100. Barlik: *Arch. f. Klin. Chir.*, 176, 657, 1933.
101. Laird, Brugh, Wilkerson: *Ann. Surg.*, 84, 703, 1926.
102. Rous, Larrimore: *J. Exp. Med.*, 32, 249, 1920.
103. Colbeck: *Guy's Hosp. Gaz.*, 46:138 and 157, 1932.
104. Petren: *Brüss. Beiter.*, 120, 501, 1920.
105. Moss: *Arch. Surg.*, 26, 1, 1933.
106. Morawitz, Herlich: *Arch. f. exp. Path. u. Pharm.*, 56, 115, 1907.
107. Wilderhaus: *Arch. f. Klin. Chir.*, 142, 698, 1926.
108. Hartmann: *Klin. Woch.*, 6, 1322, 1927.
109. Judd, Counsellor: *J. A. M. A.*, 89, 1751, 1927.
110. MacMinhon, Lawrence, Melnick: *Am. J. Path.*, 5, 645, 1929.
111. Richardson: *J. Exp. Med.*, 14, 401, 1911.
112. Counsellor: *Ann. Surg.*, 87, 210, 1928.
113. Jones and Smith: *Am. J. Physiol.*, 94, 144, 1930.
114. Quenu: *Rev. de Chir.*, 39, 462, 1909.
115. Nyro-Robson: *Brit. Med. J.*, 1:901, 1894.
116. Arnsperger: *Brüss. Beiter.*, 48, 673, 1906.
117. Clute: *Surg. Clin. No. Am.*, 13, 609, 1933.
118. Howell, Holt: *Am. J. Physiol.*, 47, 328, 1918.
119. Kerr, Horwitz, Whipple: *Am. J. Physiol.*, 47, 379, 1918-19.
120. Doyon: *C. R. Soc. Biol.*, 68, 30, 1905.
121. Lawson, Minot, Robbins: *J. A. M. A.*, 90, 845, 1928.
122. Simonis, Brandes: *Am. J. Physiol.*, 86, 623, 1928.
123. Addis: *Edinburgh Med. J.*, 6, 38, 1910.
124. Mann, Bollman: *Proc. Staff Mayo Clin.*, 4, 328, 1929.
125. Linton: *Ann. Surg.*, 96, 394, 1932.
126. Falkenhause, Sauer: *Z. f. d. ges. exp. Med.*, 67, 398, 1927.
127. Barlik: *Arch. f. Klin. Chir.*, 176, 262, 1933.
128. Barlik: *Klin. Woch.*, 13, 102, 1931.
129. Howell: *Bull. J. Hop. Hosp.*, 42, 199, 1928.
130. Clute, Veal: *Ann. Surg.*, 96, 385, 1932.
131. Rosenthal, Boensteln: *J. Lab. Clin. Med.*, 14, 464, 1929.
132. Walters: *S. G. O.*, 33, 651, 1921.
133. Ravdin: *J. A. M. A.*, 93, 1193, 1929.
134. Heyd: *Am. J. Obs. Gyn.*, 27, 356, 1931.
135. Simonds: *Arch. Int. Med.*, 23, 362, 1919.
136. Rettig: *Arch. f. exp. Path. u. Pharm.*, 76, 345, 1914.
137. Ople, Alford: *J. Exp. Med.*, 21, 1 and 21, 1916.
138. Simonds: *J. Exp. Med.*, 28, 663, 1918.
139. Simonds: *J. Exp. Med.*, 28, 673, 1918.
140. Grahnm: *J. Exp. Med.*, 21, 185, 1916.
141. Davis, Hall, Whipple: *Arch. Int. Med.*, 23, 689, 1919.
142. Chabrol, Chnrmot, Cottet: *C. R. Soc. Biol.*, 115, 835, 1934.
143. Minot: *Proc. Soc.*, 24, 617, 1927.
144. Minot and Cutler: *Proc. Soc.*, 26, 138, 1928.
145. Minot and Cutler: *J. Clin. Inv.*, 6, 369, 1928-29.
146. Dny, Armstrong: *Lancet*, 223, 1328, 1932.
147. Minot and Cutler: *Proc. Soc.*, 26, 607, 1929.
148. Juon: *Schweiz. med. Woch.*, 14, 761, 1933.
149. Ravdin, Rieck, Morrison: *Ann. Surg.*, 91, 801, 1930.
150. Hoesler, Stebbins: *J. Exp. Med.*, 29, 445, 1919.
151. Magnus: *Arch. f. Klin. Chir.*, 130, 237, 1924.
152. Stegeman: *Brüss. Beiter.*, 127, 657, 1927.
153. Thomas: *J. Mental. Science*, 74, 454, 1928.
154. Phillips, Robertson, Carson, Irwin: *Ann. Int. Med.*, 4, 1134, 1931.
155. Phillips, Robertson: *Proc. Soc.*, 26, 639, 1928-29.
156. Minot: *J. Pharm. Exp. Therap.*, 43, 295, 1931.
157. Gunther and Greenberg: *Arch. Int. Med.*, 47, 660, 1931.
158. Cruickshank: *Biochem. J.*, 17, 13, 1923.
159. Moritz: *J. Bio. Chem.*, 65, 343, 1925.
160. Reed: *J. Bio. Chem.*, 77, 547, 1928.
161. Hertz: *Biochem. Z.*, 217, 337, 1930.
162. Meyenburg et al.: *J. Bio. Chem.*, 47, 541, 1921.
163. Ray and Photak: *Am. J. Dis. Child.*, 40, 549, 1930.
164. Abt: *Pediatrics*, Philadelphia, 1923, Vol. 11, p. 417.
165. M. Herbert Barker: *Renal Clinic N. U. M. S. Personal communication*.
166. Bell: *Calif. West. Med.*, 25, 603, 1926.
167. Stewart and Leber: *Arch. Path.*, 18, 80, 1934.
168. Stewart: *Am. J. Dig. Dis. and Nutrit.*, 2, 101, 1935.
169. Chabrol et al.: *Bull. et Mem. Soc. d'Hép. de Paris*, 50, 662, 1927.
170. Czylharz, Fuchs, v. Fürth: *Biochem. z.*, 49, 120, 1913.
171. Ravdin, Johnston, Rieck, Wright: *J. Clin. Inv.*, 12, 653, 1933.
172. Greene, Walters, Fredrickson: *J. Clin. Inv.*, 9, 295, 1931.
173. McMaster, Brown, Rous: *J. Exp. Med.*, 37, 685, 1923.
174. Walters, Greene, Fredrickson: *Ann. Surg.*, 91, 6-6, 1930.
175. Rosenthal, v. Falkenhause, Freund: *Arch. Exp. Path. u. Pharm.*, 111, 170, 1926.

## SECTION IV—*Roentgenology*

### Appendiceal Abscess: A Roentgenologic Consideration, with Especial Reference to the Diagnostic Difficulties and Its Differential Diagnosis \*

By

MAURICE FELDMAN, M.D.  
BALTIMORE, MARYLAND

**A**CUTE suppurative appendicitis is quite a common affection, occurring frequently in most busy clinics. The acute type of appendiceal disease is rarely roentgenographed, not only because the clinical diagnosis as a rule is made with ease, but also due to the fact that the roentgen examination offers but little aid in the diagnosis. The acute form of this disease will therefore not be considered here. In this presentation we are primarily concerned with the chronic type, as a result of a suppurative infection, which has perforated the appendix and has become walled off, producing a localized abscess with tumor formation.

While chronic abscess of appendiceal origin with formation of a mass is not a common complication, it may present a major problem in differential diagnosis, requiring a painstaking roentgenologic investigation. The incidence of this complication varies considerably in different clinics. Adams (1) records a series of 25,000 operations for appendicitis in which there were only 45 localized appendiceal abscesses. Robinson (2) on the other hand found 46 cases of abscess in 979 operations for appendicitis, while Campbell (3) records an incidence of 16.7 per cent in his study of appendiceal abscess. Our roentgenologic experience indicates that chronic abscess of appendiceal origin is not commonly observed in the roentgen laboratory. Appendiceal abscess may often be mimicked by a rather large group of affections occurring in the right lower quadrant, presenting similar roentgenologic findings, which may produce a picture often difficult to interpret. Similarly, the clinical picture of this type of case likewise is difficult to differentiate from other tumefactions but with a more accurate appraisal of the roentgen signs, together with the clinical manifestations, the diagnosis of appendiceal abscess is far more easily facilitated. This subject therefore is of sufficient interest to warrant a brief communication, emphasizing anew its roentgenologic characteristics.

In the extensive literature on appendicitis, the scarcity of information regarding the peculiar roentgenologic characteristics of appendiceal abscess is striking. A survey of the more recent literature likewise reveals but few roentgenologic studies of this complication. The roentgen findings have been described by

a number of observers, notably by Pohl (4), Westernborn (5), Ritvo (6), Lundberg and Lilja (7), Arnell (8), Schwartz (9) and Avellan (10).

The origin of a mass in the right iliac fossa presents many difficulties in interpretation. Its close relation to the terminal ileum, cecum and ascending colon, to which it is often attached, frequently gives rise to the impression of a malignant tumor. While tumors arising from the pelvis may frequently produce similar roentgenologic findings that are confusing, the clinical, roentgenologic and pelvic examinations aid in establishing its origin. In most instances, however, a tumor in the right iliac fossa is most difficult to diagnose from a clinical and physical examination alone, but the true nature of the mass may be frequently disclosed by a thorough roentgenologic investigation. At times, even this examination may not reveal the classical roentgen picture of appendiceal abscess. The exact nature of the mass and its origin in some instances is therefore not always possible to determine until surgical investigation and pathologic studies are made. It is interesting to note that inflammatory masses in the right iliac fossa may be other than appendiceal in origin. Hypertrophic ulcerative stenosis of the ileum (12) and pericecal abscess due to a foreign body and retroperitoneal abscess often produce inflammatory masses not infrequently simulating appendiceal abscess.

The roentgen investigation, on the other hand, often will definitely establish the origin of the mass as being either an intrinsic or extrinsic colonic tumor, pointing directly to its situation and relation to the gastrointestinal tract. It will, in most instances, reveal its location better than any other procedure with the exception of surgery. The roentgen examination produces a definite group of signs in many instances, especially when the mass is of large size. Of the smaller masses and those situated in the retrocecal, retrocolic and retroperitoneal areas, in the pelvis, or distant from the right iliac fossa, the roentgen signs are very often of an indefinite nature, or may be frequently absent.

The following roentgen signs are most commonly encountered in the classical picture of appendiceal abscess. (a) Tumor mass, (b) pressure defects, (c) elevation and displacement of the ileum and cecum, (d) fixation of the ileum and cecum, (e) hyperirritability, hypermotility, (f) cecal spasm, (g) sensitiveness and tenderness, (h) inflammatory changes with

\*From the Department of Roentgenology, Sinai Hospital, Baltimore, Md.  
Submitted June 1, 1935.

alteration in contour of the cecum, (i) ileocecal patency and changes in the ileum and (j) non-visualization of the appendix.

A palpable tumor mass may be noted in many instances, but the absence of a palpable mass does not however exclude the presence of this complication. In most cases, the examination of the colon by means of the progress meal, barium enema and air insufflation of the bowel are usually sufficient to establish all the necessary data for an accurate diagnosis of tumors in the right iliac fossa. The mass and its effect upon the ileum and cecum may be more completely depicted by utilizing all of the roentgen procedures. The abscess completely may be encapsulated or it may communicate with the cecum or neighboring organs. The determination of the presence of an abscess mass, its size, shape, mobility, position and its relation to the contiguous organs are disclosed in a most striking manner by means of a thorough roentgen examination. The mass varies in size, is frequently small, but may attain huge proportions, ordinarily easily palpable, rounded, circumscribed, often spherical and frequently sensitive or tender on pressure. The tumor mass is usually fixed, but may be movable in some instances; it is homogeneous but not always dense enough to cast a shadow on the roentgenogram. Appendiceal abscesses are usually single, but multiple types have been reported by some observers (7). The position of the abscess is most commonly observed at the tip or apex

of the cecum, it may however, be noted on either side of the cecum, retrocecal or be retrocolic. A tumor mass with its origin outside the colonic tract often produces some deformity and displacement of the adjacent organs. The mass must attain sufficient size in order to produce displacement, but in most instances where a mass is palpated the displacement is quite marked. The mass frequently involves the contiguous viscera together with the peritoneum and omentum. There may be dense adhesions and also coils of small intestines involved in the mass. It may occupy any part of the abdomen; when large it may extend to the bladder, sigmoid or even the rectum. It may also be found in the pelvis, to the left side of the abdomen and in the hepatic area. The abscess may float freely in the abdomen (19). Homans and Powers (11) observed that, when an abscess appears to be in an unusual position, it is the appendix which is ordinarily displaced and not the cecum. The tumor mass and the inflammatory thickened omentum may obliterate the shadow of the psoas muscle and in rare instances a scoliosis of the lumbar vertebra may be observed.

In all instances where a mass is palpated, a "scout" film of the abdomen should be taken. This will occasionally reveal the mass, the presence of a fluid and air level and increased amount of gas in the small and large bowel. Arnell (8) points out that post-appendiceal abscess may be diagnosed without contrast filling by visualizing a large diffuse shadow surrounded by gas filled loops of intestine. Occasionally it may become necessary to take a roentgenogram in the upright posture in order to visualize a fluid level within the abscess. Frequently, however, in the chronic abscess following resolution, only a small amount and, at times, no pus may be found and therefore no fluid level may be observed. The importance of obtaining many views in different positions during the roentgenologic studies must be emphasized.

In chronic appendiceal abscess with tumor formation, a pressure defect is nearly always produced on the contiguous organs. The size of the defect varies considerably, depending largely upon the size and mobility of the mass. The defect most frequently involves the tip of the cecum and terminal ileum. The ascending colon and other segments of the bowel also may occasionally reveal the presence of a displacing defect. The defect is usually smooth, rounded, evenly distributed, frequently producing an elliptical pressure sign. The defect, however, in many instances may be very small and irregular often producing the roentgen picture of an intrinsic lesion. Pressure defects may not always be observed in the cecum. The defect depends in a large measure upon the close proximity of the mass to the cecum. Defects due to fecal material, insufficient amount of opaque medium and those from organic diseases carefully must be eliminated.

The tumor mass frequently produces a displacement and elevation of the ileum, cecum and ascending colon. A large mass in the right iliac fossa has a tendency to elevate the mobile portion of the bowel. Elevation and displacement not always may be observed as this depends in a large measure upon the position and size

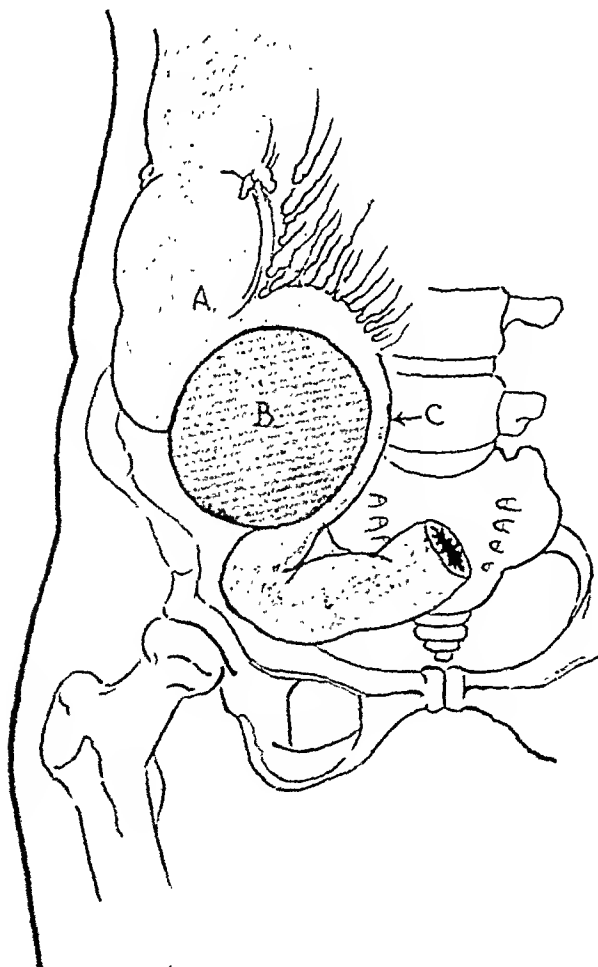


Fig. 1

Fig. 1. Drawing, demonstrating the characteristic roentgenologic picture of appendiceal abscess. a. Cecum elevated, tip narrowed and compressed. b. Tumor mass, compressing cecum and ileum. c. Ileum narrowed and compressed by the mass.



of the mass. Displacement of other segments of the bowel as well as other structures may be occasionally disclosed.

An inflammatory mass in the right iliac fossa usually is found to be fixed. Dense adhesions with involvement of the peritoneum and omentum frequently produce marked fixation. The terminal ileum and cecum are often attached to the mass, resulting in fixation of these segments of the bowel.

In most inflammatory lesions that occur in the right iliac fossa, hyperirritability and hypermotility are prominent roentgen signs. In the progress meal examination, the barium often flows through the right colon with great rapidity. The barium is observed to fill the ileum, the cecum most often is poorly filled on account of its rapid emptying, while the remaining large bowel may be well filled. Occasionally Stierlin's phenomenon may be observed: this shows a lack of filling of the cecum, and gives the impression that the barium passes directly from the ileum into the ascending colon. Hyperirritability and mass hypermotility, producing rapid emptying of the cecum, may be frequently observed following the expulsion of the barium enema.

As a result of a low-grade inflammatory process of the right colon, which is not uncommonly associated with appendiceal abscess, spasm of the cecum and ascending colon frequently may be observed. Spastic contractions of the cecum and ceco-colon may be persistent or intermittent. Considerable significance must be attached to localized spasm occurring in the right colon and according to Gershon-Cohen (17) it is probably one of the earliest manifestations resulting from inflammatory conditions. This phenomenon likewise may be produced as a reflex condition from the inflamed area. Cecal spasm is well illustrated in many instances following the barium enema and air insufflation examinations. This sign is not always observed in appendiceal abscess and it may be reproduced by any inflammatory lesion in the right bowel.

Hypersensitiveness and tenderness may be elicited in the right iliac fossa. The tumor mass is most often sensitive or tender on pressure.

In the encapsulated abscess, changes in form of the cecum is the most constant sign. This is due to the mass pressing upon the cecal wall. The cecum usually remains regular, which, according to Pohl (4), is a very important sign in the differentiation from primary lesions of this portion of the bowel. However, notwithstanding the ordinary regularity of the cecum in this condition, irregularities associated with appendiceal abscess frequently are encountered. In some instances, the tip or apex of the cecum may reveal a distinct irregularity; it may become narrowed as a result of a hyperplasia, presenting a roentgenologic picture of a narrowed tube. Although marked inflammatory changes in the cecum are unusual they may occur associated with appendiceal abscess. The ascending colon and rarely the proximal transverse colon may be occasionally involved. The inflammatory reaction may produce extensive changes in the right bowel; this is roentgenologically portrayed by narrowing of the lumen, loss of haustration and rigidity of the colonic wall, signs not unlike those observed in ulcerative colitis.

Patency of the ileocecal opening is a common roentgen finding in affections of the right bowel. This is especially observed in inflammatory lesions and is therefore not an uncommon finding in appendiceal ab-

scess. However, patency is of little significance since it occurs in the normal. Changes in the terminal portion of the ileum are frequently found, such as widening of the ileocecal opening, fixation, and also constrictions, signs resulting from an inflammatory process. Hyperplasia surrounding the ileocecal area frequently produces a deformity of this segment. The terminal ileum is often infiltrated, and thickened, frequently forming part of the abscess.

The appendix is not as a rule visualized. The relation of the abscess to the appendix is variable as the perforation may occur at any point. The whole appendix may be gangrenous and form part of the abscess, the appendix lying within it. The appendix usually forms part of the inflammatory mass. Frequently it is buried in the cecal wall. If the abscess communicates with the appendix or cecum, the abscess cavity may become filled with barium. This finding, however, is of rare occurrence.

The routine examination by means of the gastro-intestinal progress meal reveals certain roentgenologic findings which are often quite essential in the study of appendiceal abscess. Information not only is given by this method as to the functional state of the bowel, but also the anatomic relationship of the mass to the adjacent organs. The abnormal motility of the right bowel especially is depicted. Evidence of increased irritability is also clearly portrayed by this procedure. This examination likewise may aid in the differential diagnosis of the many obscure conditions which occur in the right lower quadrant. In some instances the progress meal examination may fail to reveal the presence of an abscess and the case may go undiagnosed, until perhaps a barium enema investigation is undertaken.

The barium enema examination often discloses extremely valuable information in appendiceal abscess which information cannot be determined by other means. The barium is observed to flow up the bowel readily until it reaches the cecum, where distinct roentgen changes are often depicted. The cecum may or may not become completely filled, often shows evidence of pressure, irregularities, increased irritability, rapid emptying and ileocecal patency; these produce a filling of the terminal portion of the ileum. Evidence of an inflammatory process of the cecum may be likewise observed. The mass usually is palpated during this examination and its relation to the cecum and ileum can be determined. The fluoroscopic examination of the right iliac area is especially important to determine the relation of the distorted portions of the ileum and cecum. This procedure is one of the most essential steps in the investigation of the appendix area in order precisely to disclose the exact location of the mass as well as to determine whether or not it is within or outside the intestinal tract. The ileum and ileocecal opening is also best studied by this procedure.

The barium enema frequently produces a typical, classical, characteristic roentgen picture of appendiceal abscess. The barium is allowed to flow into the bowel slowly and a meticulous study is made of the area surrounding the mass. The cecum may show but little evidence of inflammation. Appendiceal abscess may or may not produce inflammatory changes in the adjacent organs. When the ileum, cecum, ascending and transverse colon are affected by inflammatory changes, the diagnosis becomes increasingly more difficult, inasmuch as other infections produce similar roent-



Fig. 2a

Fig. 2a. Roentgenogram (barium enema), illustrates a case of appendiceal abscess. Cecum elevated; narrowing of cecal tip and fixation of wall of ileum is shown at arrows. (case proven at operation).



Fig. 2b

Fig. 2b. Shows marked irritability of the bowel, with rapid emptying of the cecum. Note large amount of barium retained in the ileum.



Fig. 3a

Fig. 3a. Ragged appearance of the tip of the cecum is shown at arrows. Cecum is elevated; the extreme cecal tip is narrowed; the terminal ileum is narrowed and fixed. (appendiceal abscess found at operation).



Fig. 3b

Fig. 3b. Illustrates marked hyper-irritability of the cecum, with rapid emptying, a frequent sign of an inflammatory process.

manifestations. It must be borne in mind that the roentgen examination of the colon may not always disclose any sign in the cecum which might indicate the presence of an appendiceal abscess, especially when it is very small, or in instances where it is situated distant from the cecum. When a mass is palpated, it is of paramount importance to determine its relation to the ileum and cecum. Frequently a pressure defect is observed producing an upward displacement of these segments of the bowel. The resulting pressure usually produces a smooth regular defect, but does not as a rule reveal roentgen evidence of an infiltrating affection.

A small persistent irregularity, or filling defect, or incomplete filling of the tip of the cecum is strongly suggestive of an appendiceal abscess, but great caution should be taken in interpreting this finding. When the cecal tip is poorly filled following a barium enema. Even in the absence of a palpable mass, the possibility of this complication should be considered. Filling defects occurring in the cecum are often confused, because of the marked similarity of the roentgen findings produced by other affection occurring in this area. It should again be emphasized that when a mass is palpated in the right iliac fossa, it may not always be due to an appendiceal abscess inasmuch as other lesions are frequently encountered in this area which mimic those of an abscess.

After studying the bowel by the usual roentgen methods, it may occasionally become necessary to make further investigations in order to study the origin of the mass. The introduction of air into the bowel may be quite helpful in some instances in delineating the mass and adjacent organs. Spasm and irritability of the cecum also may be observed in this examination as well as displacement due to the tumor.

Pneumoperitoneum has been mentioned as a procedure for visualizing abdominal tumors. In our opinion this method of examination is dangerous in the presence of inflammatory masses.

There are many diagnostic difficulties encountered in the study of this complication. This is no doubt due in a large measure to the varying roentgen picture, so commonly observed in appendiceal abscess. As mentioned before, this affection may not reveal any sign whatever which might indicate its presence, or on the other hand there may be minimal roentgen signs that are too indefinite to point to the exact nature of the condition; then again a large pressure defect may be depicted in the cecum indicating the presence of an extrinsic mass. These variable roentgenologic findings observed in appendiceal abscess make this condition at times one of the most difficult to interpret. However, it is often possible to make a correct diagnosis together with the clinical findings, but, even here, the exact diagnosis of the true nature of the mass cannot always be made with certainty.

In the appraisal of the roentgen signs of appendiceal abscess consideration of a group of other lesions occur-

ring in the right iliac fossa must be considered in the differential diagnosis. The key to this diagnostic study is first to determine whether the lesion is localized, second, whether or not it is within or outside the bowel and third, whether or not it is an infiltrating tumor. The most common conditions which must be considered in the differential diagnosis are: benign and malignant tumors of the appendix, carcinoma of the cecum, hyperplastic (13) and hypertrophic (18) tuberculosis, retroperitoneal tumors, abscess, enlarged or abscessed glands, non-specific granulomata involving the ileum and cecum (12), ileitis (20) and other inflammatory conditions, psoas abscess, psoas tumors, pelvic tumors, peri-nephritic abscess, ectopic kidney (16), kidney tumors, hydrops of gall bladder (14), mesenteric tumor or abscess, abscess due to a foreign body, inflamed omentum with adhesions (16), amebic infection, ileocecal invaginations, fungus infections (4), and right sided diverticulitis.

Of the above conditions which may closely mimic appendiceal abscess, the most commonly encountered which often require special consideration are, carcinoma of the cecum, ileo-cecal tuberculosis, retroperitoneal masses and tumors arising from the pelvis.

#### SUMMARY

Appendiceal abscess produces a mass in the right iliac fossa which often creates a great deal of discussion in the interpretation and differential diagnosis. The extreme variation in the roentgen picture from little or no roentgen signs to a large group of signs is the most important factor, which accounts for many of the difficulties and errors in diagnosis. It is likewise mimicked by a large group of conditions which require painstaking study in the differential diagnosis. On the other hand, appendiceal abscess frequently produces a roentgenologic picture of an extrinsic mass which is closely attached to the ileum and cecum, often producing changes in these segments of the bowel suggestive of an inflammatory process. Since it involves the contiguous organs one may often interpret these findings as due to an appendiceal abscess. The roentgen examination is quite important in determining whether or not the mass is intrinsic or extrinsic. This however, is not always possible, especially when there are minimal changes in the cecum.

The roentgen signs of appendiceal abscess are at times quite characteristic, revealing a pressure defect, inflammatory changes in the ileum and cecum, hypermotility and hyperirritability of the right bowel and the presence of a tender mass in the right iliac fossa. One must on the other hand, be aware of the many conditions which simulate this complication and make the differential diagnosis with some caution, inasmuch as it is often difficult to state the exact nature of the mass. The roentgen examination offers the best means for investigation of appendiceal abscess and its differential diagnosis. When considered with the clinical findings, the diagnosis may be made in a large percentage of cases.

#### REFERENCES

1. Adams, D. S.: Appendiceal Abscess. Operation without removal of the Appendix. *New Eng. J. of Med.*, 208:123, Jan. 19, 1933.
2. Robinson, C. M.: Discussion of Adams paper. *New Eng. J. of Med.*, 208:126, Jan. 19, 1933.
3. Campbell, J. L.: Appendiceal Abscess. A Clinical Study. *South. Med. Jour.*, 7:653, 1914.
4. Pohl, R.: Postappendicitische Abszesse in Röntgenbild. *Fortschr. a. d. Geb. d. Röntgenstr.*, 42:19, July, 1930.
5. Westerborn, A.: The Importance of Roentgenologic Examination in Acute Cases of Circumscribed or Diffuse Peritonitis. *S. G. O.*, 52:804, 1931.

6. Rizzo, M.: The X-ray in the Diagnosis of Appendiceal Abscess. *Boston M. & S. Jour.*, 197:307, Aug. 25, 1927.
7. Lundberg, S., and Lilia, B.: Three Cases of Intraperitoneal Multiple Abscess Formation After Appendicitis Where Radiographic Examination Enabled Abscesses to be Diagnosed, Impossible of Being Localized by Clinical Methods. *Acta. Chir. Scan.*, 64:557, April 23, 1929.
8. Arnell, S.: Roentgenological Signs of Appendiceal Abscess. *Acta Radiologica*, 12:759, Sept. 30, 1931.
9. Schwartz, I.: X-ray Findings in a Case of Appendiceal Abscess of One Year's Duration. *Radiology*, 6:432, 1926.
10. Avellan, J. A.: Roentgenologic Visualization of Appendiceal Perforation. *Am. J. Surg.*, 8:427, Feb., 1930.
11. Homans, J., and Powers, J. H.: Appendiceal Abscess: Treatment of the Appendix. *New Eng. J. Med.*, 199:319, 1928.
12. Ginsburg, L., and Oppenheimer, G. D.: Non-specific Granulomata of the Intestines (Inflammatory Tumors and Strictures of the Bowels). *Ann. Surg.*, 95:1016, 1933.
13. McMullin, J. J. A.: Hyperplastic Tuberculosis of Cecum Simulating Appendiceal Abscess. *U. S. Naval Med. Bull.*, 29:244, 1931.
14. Bjorkenkeim, E. A.: Hydrops of Gall Bladder Simulating Appendiceal Abscess. *Zentralbl. f. Gynak.*, 54:597, 1930.
15. Ikeda, Kuno: Unusual Experience with Amebic Dysentery. *J. J. M. A.*, 101:1944, 1933.
16. Stein, A.: Diagnostic Difficulties of Appendiceal Abscess. *Med. J. & Rec.*, 199:260, 1928.
17. Gershon-Cohen, J.: The Diagnosis of Early Ileocecal Tuberculosis. *Am. J. Roentgenology*, 24:367, 1930.
18. Davis, A. A.: Hypertrophic Intestinal Tuberculosis. *S. G. O.*, 56:207, 1933.
19. Perkins, E. J., and Hepp, L. C.: Unusual Appendiceal Abscess. *Colorado Med.*, 29:331, 1932.
20. Crohn, B. B., Ginsburg, L., and Oppenheimer, G. D.: Regional Ileitis. *J. A. M. A.*, 99:1323, 1932.

## ABSTRACTS

JULIAN M. RUFFIN AND DAVID T. SMITH, DURHAM, N. C.

*The Treatment of Pellagra with Certain Preparations of Liver.* Vol. 187, pp. 512-521, April, 1934.

On the basis of thirty-seven cases of pellagra, fourteen of which were used as controls, certain interesting conclusions are reached as to the effectiveness of liver therapy. The fourteen control cases were treated by a diet containing known and adequate anti-pellagra factors which had previously proven to be effective in the cure of the disease. The cases in which liver therapy was instituted were placed on a diet similar to that which they had been taking prior to the development of symptoms. This diet contained adequate amounts of fats, proteins and carbohydrates, minerals and all the known vitamins, except Vitamin G (B<sub>7</sub>). Patients with pellagra reported in this series did not improve on this diet. However, when this group was put on an aqueous extract of liver in doses of 90 c.c. daily by mouth; or given a powdered extract of liver in doses of 3 vials daily; or given an insoluble residue derived from the alcoholic extraction of an aqueous extract of liver, prompt abatement of symptoms ensued with eventual cure. Five cases on this same diet lacking only in vitamin G (B<sub>7</sub>) failed to improve when treated with liver extract No. 343 intramuscularly in doses of 5 c.c. daily.

When the oral aqueous extract of liver was substituted for the intramuscular extract in this same group of five, a dramatic clinical improvement began between the third and fifth day, and continued until the patients were apparently well.

Evidence is presented indicating that the bilateral symmetry of the skin lesion is due to bilateral exposure to sunlight, as in this series it was shown that unilateral lesions can be produced by unilateral exposures.

MILLER, D. K., AND RHOODS, C. P.

*"The Vitamin B, and B2G Content of Liver Extracts and Brewers' Yeast Concentrate."* *J. Exper. Med.*, 59:315-330, March, 1934.

A series of growth experiments on rats, using liver extract powder or vegex as a source for B1 and Brewers' yeast for B2G. The results in rats indicate that growth is not adequate with B1 alone, especially when the liver extract is given by intraperitoneal injections. The addition of B2G in these experiments results in a return to and maintenance of normal growth. The authors conclude that the extrinsic antianemic factor described by Castle is not identical with the thermostable growth producing vitamin B2G.

M. G. V.

## SECTION V—*Therapeutics*

### A Symposium on Management of Oesophagitis

#### Article I

**M**Y general plan in the therapy of oesophagitis is as follows:

1. The first thing in the morning, to cleanse out collected mucus, sodium bicarbonate, 2 Gm. (30 grains), in a glass of water, to be sipped down in five or ten minutes. This either softens the mucus and carries it into the stomach or the solution is regurgitated with the mucus. In either event the subsequent swallowing of food is facilitated.

2. About twenty minutes before each feeding the patient sucks an unsweetened lozenge containing 0.13 Gm. (2 grains) of aethyl aminobenzoate. This promises sufficient anesthetic effect to allay pain and spasm when food is swallowed.

3. One hour after each feeding the patient swallows bismuth subcarbonate, 1.3 Gm. (20 grains), in a very small amount of water; this acts to coat the inflamed area.

4. The diet at the outset is of the bland, highly vitaminized peptic ulcer type, but when the stomach is not involved the feedings are much larger in quantity and are spaced further apart than they are when ulcer is present.

Walter A. Bastedo, New York City.

#### Article II

##### A. ACUTE OESOPHAGITIS

Application of ice bag to sternum and neck. Allow bits of ice to be dissolved in the mouth. Administer olive oil containing bismuth subcarbonate by mouth. (Two teaspoonsful of olive oil with a suspension of ten grains of subcarbonate of bismuth every three or four hours). In severe types, intravenous glucose feedings and water by bowel or subcutaneously and nothing by mouth. When the patient is better, allow ice cold milk by mouth in teaspoonful doses and gradually increase; then soft food after a time. When pain on swallowing is extreme, dissolving othoform or anesthesin lozenges in the mouth and swallowing the saliva is beneficial.

When the lesion is acute (as following the swallowing of poisons) a duodenal tube may be kept in situ (or a Levin tube) and all feeding and medication given through the tube, except protective medicines as oils, suspensions of bismuth or local anaesthetics as orthoform.

##### B. CHRONIC OESOPHAGITIS

When due to the abuse of alcohol, alcoholic drinks should be prohibited. In other forms, when due to disease of the lungs and heart, the main treatment should be directed to the primary lesion. Tobacco and hot fluids should be avoided; bland, cold diets may be

given, especially ice cold milk taken in small amounts at frequent intervals. A smooth diet is permissible.

A one per cent solution of nitrate of silver or tannic acid may be applied through a catheter. Olive oil in tablespoonful doses and bismuth in small amounts taken three or four times daily are valuable.

The following prescriptions will be of service:

| 1.                        | 2.                          |
|---------------------------|-----------------------------|
| Acidi Tannicae grs. V     | Argent. Nitrate grs. V      |
| Ol. Olivae oz. II         | Ol. Olivae oz. II           |
| Shake label. Sig.: 30     | Shake label. Sig.: 30       |
| drops in little cool milk | drops in a dessert spoonful |
| 4 times daily.            | each of cool milk and       |
|                           | glycerine 4 times a day.    |

These are to be taken only for a short time.

Julius Friedenwald, Baltimore.

#### Article III

##### MANAGEMENT OF OESOPHAGITIS

Consideration of the etiology of oesophagitis forms the basis for rational therapeutic procedures. The chief subjective symptom is "heart burn."

Normally the acid gastric juice does not come in contact with the lower end of the oesophagus. Frequent regurgitation of stomach contents and vomiting irritate this sensitive area and a chronic inflammatory process results. In severe cases, as emphasized by Chevalier Jackson and his co-workers, peptic ulcer is formed.

The dietetic treatment is quite similar to that of gastric and duodenal ulcer. The food must be soft and fiber-free and should be served cool. All hot drinks and condiments must be avoided. Petrolagar (plain) is useful in doses sufficient to prevent constipation; it also acts as a protectant to the irritated, engorged oesophageal mucosa.

The patient must be instructed to "control belching." Immediately after eating and whenever an uncomfortable feeling of fulness or distention is experienced, he must take a series of deep breaths with special emphasis upon exhalation. The vigorous action of the diaphragm tends to force the stomach "gas" out of the pylorus instead of permitting it to escape at the cardia.

Alkalies are rarely indicated, sodium bicarbonate especially is prone to favor eructations of gas which may draw acid contents into the inflamed area.

The Author often gives small doses of atropine sulphate (grain 1/500) in tablet form, every six hours with the idea of assisting the cardia in regaining its functional tonus.

Ambulant treatment is preferable to bed rest. Eructations are more likely to occur when the patient is in the recumbent posture.

Horace W. Soper, St. Louis.

## SECTION VIII—*Editorial*

*NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastroenterological Association is in no way responsible for editorial expressions.*

In January, 1935, *The Spanish Journal of Diseases of the Digestive Apparatus and of Nutrition (Revista Espanola de las Enfermedades del Aparato Digestivo y de la Nutricion)* began publication in Madrid, Spain, by the house of Espaso-Calpe, S.A., Rios Rosas, 26—Apartado 547. The Editorial Committee comprises over 20 well known Spanish gastro-enterologists and the directing committee is composed of S. Carro, T. Hernando, E. Oliver, and H. G. Mogená. The foreign subscription rate is 40 pesetas (\$5.10 at present). The material printed each month consists of original articles, Editorials, abstracts and Book Reviews. The journal is well-printed and well-illustrated. All Editorials and abstracts are signed by the authors. Conservative advertising and an attractive format, as well as the obviously high-grade editorial material used, promise a long future for this publication.

The American Journal of Digestive Diseases and Nutrition extend congratulations and best wishes for long-continued success to its sister Journal.

The Editorial Council.

### AMERICAN BOARD OF GASTROENTEROLOGY

**I**NQUIRIES are constantly being received regarding the activities of the American Board of Gastroenterology. Many are openly critical of the inactivity of the Board, the correspondents feeling that, with the large influx of incompetent practitioners calling themselves "stomach specialists," a method of "dividing the sheep from the goats" is urgently needed. These individuals feel that issuing certificates to qualified gastroenterologists is all that is required to accomplish this end.

The problem, however, is not so simple as it seems. Some of the already functioning qualifying boards have found themselves in difficulties. No board can compel a practitioner to take its examinations and no patient can be coerced into consulting only the experts approved by a board. To have each board or even a co-ordinating board advertise to the public would not only involve a prohibitive expense but would probably be considered unethical. It has been realized for some time that the American Medical Association is the only organization that could control the whole situation adequately, and, in the past few years, definite steps have been taken to insure its controlling or actually taking over the activities of the existing boards as well as the organization of new boards.

The American Board of Gastroenterology, organized over a year ago by the two recognized national gastroenterological organizations—The American Gastro-Enterological Association and the Section on Gastro-

enterology and Proctology of the American Medical Association—and composed of members from different parts of the country, had its annual meeting in Atlantic City on June 12, 1935, during the week of the American Medical Association meeting. The report of its president is published below. It expresses the belief of all the members of the Board that it would be well not to attempt to force the issue with the American Medical Association, but to await the approval, co-operation or even actual control of the certification of gastroenterologists by the American Medical Association. The By-Laws of the Board, conforming to the standards set up last year by the Council on Medical Education and Hospitals of the American Medical Association, absolutely require that candidates for examination shall have had training in schools, hospitals, clinics and laboratories approved by the American Medical Association Council as being competent in gastro-enterological work; also its fundamental requirement is that all candidates first must be qualified internists. Qualification of internists has not yet been accomplished, but the Section on Internal Medicine of the American Medical Association has just appointed a Committee to meet with a similar committee of the American College of Physicians to form a Board of Internal Medicine. Prominent internists who have hitherto opposed the recognition of gastroenterology as a specialty have expressed approval of this requirement of our Board and in the future we can expect an increasing interest in and support of our stand namely, that a qualified internist has the right to limit his (or her) practice to gastroenterology as a specialty, that such a person has the right to be considered a specialist and that the standards of the specialty must be maintained by the application of the principles expressed in the By-Laws of the American Board of Gastroenterology.

A. F. R. Andresen, Brooklyn.

### REPORT OF THE PRESIDENT

Following the organization of our Board on June 14th, 1934, with the adoption of By-Laws and the election of officers, the seven members then present went before a notary and signed original and duplicate copies of the Articles of Incorporation. Your President then wrote to the secretary of the Advisory Board for Medical Specialties calling his attention to the fact that the House of Delegates of the American Medical Association had instructed the Council on Medical Education and Hospitals to add Gastroenterology to the list of specialties approved for the certification of specialists and informing him that we would soon make application for approval by the Advisory Board. Some lively correspondence ensued, the Advisory Board contending that our Board had used crooked politics in



having the resolution passed by the House of Delegates and your President pointing out that the resolution had been passed in the regular way, following an open hearing at which the Council on Medical Education and Hospitals had had numerous representatives, and that the real purpose had been to enable the Advisory Board to confirm its previous approval of our Board.

In July, 1934, a meeting of the Board of Regents was held at the office of B. B. Vincent Lyon in Philadelphia, the three members necessary for a quorum to transact business being present (Doctors Gaither, Boekus and Andresen). At this time it was decided that the Board should not make any further efforts to gain the cooperation of the Advisory Board, but should confine its efforts to recognition by the Council on Medical Education and Hospitals of the American Medical Association. It was also decided that incorporation should not be completed until our Board had the complete approval and cooperation of the Council. At subsequent meetings in October, 1934, and January, 1935, this stand was further approved by our Board of Regents and by the Council of the American Gastro-Enterological Association.

Meanwhile, the Council on Medical Education and Hospitals has been studying the whole subject of certification of specialists, with a view to supervising or perhaps taking over this work. In a personal interview with Doctor W. D. Cutter, Secretary of the Council, last December, he assured your President that a careful and prolonged study was under way, and that the Council was not contemplating the recognition of the Advisory Board nor of any specialty Boards until the study was completed and a definite course of action had been decided upon. Your President then offered the full cooperation of the American Board of Gastroenterology in any way that the Council might see fit to use its experience and prestige in the furtherance of the aims of the Board as expressed in its By-Laws. Aside from encouraging gentle suasion and pressure on those in authority in the American Medical Association to make them favorable to our Specialty, no further work has been done. The efforts of the Board should now be directed to the establishment of recognized post-graduate courses in gastro-enterology in schools, hospitals and clinics.

A. F. R. Andresen, Brooklyn,  
President American Board of Gastroenterology.

#### REPORT FROM AMERICAN BOARD OF GASTRO-ENTEROLOGY TO THE SECTION ON GASTRO-ENTEROLOGY AND PROCTOLOGY OF THE AMERICAN MEDICAL ASSOCIATION

**I**N accordance with a resolution jointly passed by the Section on Gastro-enterology and Proctology of the American Medical Association and the American Gastroenterological Association each appointing committees of four members with instructions to form such a Board and to serve upon it, the American Board of Gastro-enterology was organized on June 14, 1934, at Cleveland, Ohio. A set of By-Laws, which previously had been approved by the Advisory Board for Medical Specialties and which conformed in every way to the requirements of the Council on Medical Education and

Hospitals of the American Medical Association, was adopted, and the following officers were elected:

President, Albert F. R. Andresen, Brooklyn.  
Vice-President, Franklin White, Boston.  
Secretary-General, Ernest H. Gaither, Baltimore.  
Treasurer, Frank Smithies, Chicago.

Additional Members of Board of Regents  
Henry L. Bockus, Philadelphia.  
George B. Eusterman, Rochester, Minn.  
Sidney K. Simon, New Orleans.  
Adolph Sachs, Omaha.

On the same day, the House of Delegates of the American Medical Association, after a hearing and on recommendation of its committee on Education, passed a resolution instructing the Council on Medical Education and Hospitals to add Gastroenterology and Proctology to the list of specialties approved for certification of specialists. Since this time the Council has been investigating the entire subject of certification and has not yet actively entered this field, although, logically, it may be expected eventually to include the certification of specialists in all fields among its manifold activities.

In view of the fact that the rules of our Board applying to the qualifications of candidates for certification, the investigation and approval of schools, hospitals and clinics engaged in post-graduate work and the publication of lists of such schools and specialists, requires the cooperation of and in fact control by the Council on Medical Education and Hospitals, the members of the American Board of Gastroenterology have decided that the Board shall not begin to function without the full approval and cooperation of the Council and have offered their services to the Council in an advisory capacity. The efforts of organized gastroenterology should now be directed to the establishment of recognized post-graduate courses in gastroenterology.

#### CHOLESTEROL

**R**ECENT studies in the blood cholesterol are apparently destined to have a tremendous influence upon the dietary habits of man. Of special significance is a recent article by Rabinowitch (1) on "The Relationship of Plasma Cholesterol and Arteriosclerosis." He concludes that excess blood cholesterol is an important etiologic factor in the production of arteriosclerosis in the young diabetic. Also that treatment with the high carbohydrate—low calorie diet has delayed development of cardiovascular disease in the cases investigated.

The work of Timothy Leary (2) is also of great significance. He was impressed with the high content of lipoids in atheromatous aortae. Cholesterol is the only sterol found in animal bodies. It forms the framework of all animal cells. It combines with fatty acids to form esters. In our dietary, eggs, milk, and pork fats are the main sources of supply. Leary concludes that the lesions of human athero-sclerosis can be reproduced in the rabbit by feeding cholesterol. The inheritance of a poor cholesterol metabolism appears to be associated with the tendency to early death from coronary sclerosis.

Joslin (3) suspects a high cholesterol blood content as the etiological factor in cataract and arteriosclerosis in the diabetic. He emphasizes the importance of

keeping the fat in normal limits in diabetes, at least under 230 mg. of cholesterol per 100 cc. of blood.

Recent studies by Hartung and Bruger (4) are of interest. The plasma cholesterol tends to be low in rheumatoid arthritis and elevated in osteo-arthritis. These observations lend added proof to the theory that rheumatoid arthritis is an infectious disease and osteo-arthritis a degenerative one.

Lockie and Hubbard (5) in their article "Changes in Symptoms and Purine Metabolism Produced by High Fat Diets in Four Gouty Patients" conclude as follows: "The development or exacerbation of joint symptoms following the ingestion of a diet high in fat and low in carbohydrate and protein for several days may serve as a useful test in the differential diagnosis of gout. Diets high in fat and low in carbohydrates should be avoided in the treatment of patients with gout."

Perhaps the majority of internists have been in the habit of feeding a diet of low protein content in the treatment of arteriosclerosis. Others have employed the alkaline ash regime. Certainly few have considered the fats, with the exception of Joslin and his followers in their campaign against obesity as a forerunner of diabetes.

Our therapy of vascular disease should include a sharp reduction in the foods containing cholesterol. It does not require much imagination to believe that the reduction in the consumption of such foods may materially prolong life by the prevention or delay in the formation of arterial disease, particularly coronary athero-sclerosis.

The articles cited above are splendid examples of clinical research work. They have inaugurated a new chapter in preventive medicine.

Horace W. Soper, St. Louis.

#### REFERENCES

1. Rabinowitch, I. M.: "Arteriosclerosis in Diabetes." *Ann. Int. Med.*, Vol. 8, No. 11, p. 1435, May, 1935.
2. Leary, Timothy: "Experimental Athero-sclerosis in the Rabbit compared with Human (Coronary) Athero-sclerosis." *Arch. Path.*, 17:453, April, 1931.
3. Joslin, E. P.: "Fat and the Diabetic." *New England J. Med.*, 209:519, September 14, 1933.
4. Hartung, E. F., and Bruger, M.: "Cholesterol Content of Plasma in Arthritis." *Jour. Lab. and Clin. Med.*, 20:675-784, April, 1935.
5. Lockie, I. M., and Hubbard, Roger S.: "Gout: Changes in Symptoms and Purine Metabolism Produced by High Fat Diets in Four Gouty Patients." *J. A. M. A.*, Vol. 104, No. 23, p. 2072, June 9, 1935.

## SECTION IX—Book Reviews

(This section is open to contributions from any medical reader, whether a member of the Editorial Council or not).

*Radiologie Clinique du Tube Digestif, Publiée sous la Direction de Mm. Pierre Duval, Jean-Charles Roux, Henri Bécélère*; Second Edition; 372 pages with 514 radiographs and 516 schematic outlines explaining the Roentgenographic reproductions. Masson et Cie, Publishers, Paris, France. Price, to non-residents of France and its colonies, 330 francs.

**SUPERLATIVELY**, do the French perform a task when that task is worth-while, when they abandon their *laissez faire* attitude (is such but a national pose?) and when the enterprise under consideration really is along important lines or comprehends unusual pointings.

Whether the project be in clinical medicine (Laennec), microbiology (Pasteur), chemistry and physics (Dubois-Raymond), art (Corot), music (Bizet), literature (Hugo, Loti), armament (the famed "75's"), aviation (Nungesser), or the stern, blood-and bone-valor and the *flan*-demanding mouths of a Verdun hell—whatever it be which calls for whole-souled devotion, our French *confreres* have been, and yet are, capable of extraordinary, concentrated effort, magnificently delivered.

Judge not France by those individuals who smirk in the *entresol* of the Folies Bergère, who strut at Long-champs, gesticulate clownishly and jabber incoherently in the "Chamber" or dwindle on the Bois! Centuries have proved that, from the *habitant* up through the *haute monde*, there runs a fibre of steel, the flame of genius, the patience and intelligent persistence in this, a people sure of its quality and daring in its conceptions and acts. When least expected, these attributes become manifest: epoch-making results follow.

Genius, solid special knowledge, unique planning, vast technical and clinical experience, admiration-compelling perseverance and unrivalled execution are exhibited by Doctors Duval, Roux and Bécélère in their recently issued "Atlas" titled as above. Excellent as was the First Edition of this book, closer team-play, extended experience and unusual cooperation with their renowned Publishers have resulted in the production of what this reviewer considers to be the most important and useful Roentgenologic atlas yet to appear in any country.

For convenience in handling, this stupendous work is issued in two, most attractively and substantially bound volumes. Even before making a detailed study of the books' contents, one is impressed by the beautiful, yet serviceable binding, the artistic title-lettering and imprint, the large, well-printed page, the selection of type-fonts, the assembling and arrangement of material, the sharpness of the Roentgen reproductions, the appropriately-placed index. It is but proper that, before discussing the subject-matter of the volumes one, here, pay tribute to the very evident interest which the House of Masson et Cie has manifested towards enabling the distinguished Authors best to present their out-of-the-ordinary studies to an audience which, on the basis of past contributions to the literature by Drs. Duval, Roux and Bécélère, expects much. Detailed perusal of the volumes disappoints no reader with respect either format or scientific substance. Most certainly, the Authors are indebted greatly to their Publishers for such a marked degree of understanding co-operation.

The plan of presentation is logical, instructive, down-to-date, comprehensive: indeed, we have seen no work on the subject which so thoroughly covers the field. So well is the enterprise carried through that it is sure to command the interest of the general internist quite as much as that of the Roentgen specialist.

Before entering upon special discussion of affections of the stomach and the duodenum, the Authors submit a concise, but adequate chapter dealing with methods of procedure in X-ray study. In addition to listing the procedure common to Roentgenographic examinations with the aid of opaque media, they emphasize methods whereby added information about the viscera may be obtained by combining air-inflation of the organs partly filled with a bismuth-geletine composition. Air is introduced by means of a duodenal tube whose tip may lie in the stomach or in the duodenum; the opaque mixture thus is scattered over all parts of the mucosa as a thin, adherent, adhesive film; Roentgenograms, made after such technic, permit most interesting and, at times, diagnostic, studies of the mucous membrane or of ulcers or of neoplasms. The Authors present many film-reproductions throughout the work which demonstrate the value of these technical innovations.

However, complete as is this "Atlas," we observe that no great space is devoted to fluoroscopy or the advantages to the diagnostician of using localized pressure, during fluoroscopy, and then, while the lesion still is visible, making multiple Roentgen exposures from various angles. Unless we are in error, such compression-Roentgenograms made at fluoroscopy constitute one of the few basic advances of the past decade; witness the last three years' efforts of the Scandinavians. However, in an atlas seemingly devoted largely to the objective reproduction of anomalies, perhaps the Authors considered it not essential to present an elaborate discussion of what the newer fluoroscopic technic has to offer. Yet, there is exhibited so complete a Roentgen coverage of affections of the stomach and the duodenum that, the reviewer for one, would have welcomed a thorough discussion of fluoroscopy by these very evident masters of film-making and deductions therefrom.

In this work of Duval, Roux and Bécélère, the actual Roentgenographic study of the viscera in health and in disease is presented along unique lines. In all conditions possibly affecting the stomach and the duodenum, the page facing the reader carries sharp, clean-cut reproductions of Roentgen films. On the opposite page, are anatomico-schemic pen-and-ink sketches faithfully drawn to correspond with each particular Roentgenogram. These diagrammatic drawings, to the most minute degree, not alone elucidate these Roentgenograms of the filled viscera but carry accurate, concise notes explaining each feature of the film and its corresponding schemic sketch. One need but glance through a few pages to recognize the high degree of conscientious care which has been devoted to both sketches and the legends explaining them, and to the Roentgenograms to which they refer. Not alone to him who is expert in Roentgenology do these data convey a mine of clinical and technical information but to the clinician who is not concerned with the actual making of Roentgenograms, both films and their corresponding interpretative sketches comprise a series of studies invaluable instructive. Undoubtedly, the

Authors have, by their painstaking efforts, driven away from Roentgenology of the viscera considered, much of what previously has been assumed to be the peculiar knowledge of the Roentgenologist and have made it possible for the internist, who previously has been lost in the so-called mysteries of his fellow-consultants' "cult," to attain proficiency in film-interpretation with but a reasonable degree of study and application. A quip supposedly indicating the dense degree of illiteracy of the colored race, has the jovial Negro asking his Master regarding a newspaper: "Pahdon me, Boss!, but which does you-all read, de white or de black paht?" Among physicians looking at Roentgen films, one still finds those to whom the "white paht" signifies quite as little as does the "black"! In this and, doubtless other countries, perusal of this new atlas should render impossible such "film illiteracy."

In the space allotted for this review, one cannot do justice to the various sections of Drs. Duval, Roux and Bécélère's "Atlas"; each page exhibits its individual points of significance. From the Roentgenograms detailing the variations possible to the normal stomach and the duodenum, observations of essential value most strikingly are demonstrated in presentations of "Hypersecretion and Stasis"; "Aerophagia"; "Ptosis, without and with Atony"; "Cascade or 'champagne goblet' stomach"; "Visceral Deformities due to External Pressure"; "Volvulus"; "Gastritis"—an outstanding presentation of anomalies of the mucosa; "Chronic Gastric Ulcer—with a most excellent series exhibiting protected perforative types, with or without hourglass deformity"; "Pyloric Ulceration"; "Perforated Ulcers"; "Pyloric Stenosis"; "Hour-Glass Stomach"—a splendid set of examples of all forms.

It should not be gathered that the above topics are shown by Roentgenogram reproductions and schemic drawings only; on the contrary, each subject is accompanied by a sound clinical as well as Roentgenographic discussion—a procedure which adds much to the illustrations and which demonstrates, too, that the Authors are not just "picture-makers" but are clinicians of greater than ordinary acuteness. It is rather surprising that the Authors exhibit no examples of "Syphilis of the Stomach"—in fact, in a brief statement, express it as their opinions that lues causes no characteristic gastric deformities, Roentgenographically considered. It is the reviewer's experience that, when lues organically involves the stomach, the Roentgen films disclose anomalies which, in his opinion based upon a considerable series of cases, are almost pathognomonic. American clinicians and Roentgenologist would seem to have settled upon a syndrome for gastric syphilis in which Roentgenograms contribute very significant evidence; indeed, the films not uncommonly tip the scales towards the making of positive diagnoses.

Two comprehensive chapters are devoted to gastric malignancy, one to benign tumors, one to gastric foreign bodies, one to gastric diverticula, one to perigastritis, with or without its accompanying visceral deformities. An amazing lot of common and unusual material is presented and the discussions supplementing the illustrations are rich with descriptive and diagnostic data.

One of the most important sections of the work, and one concerned with most clarifying and down-to-date remarks which elaborate upon the Roentgenograms, is that dealing with "Diaphragmatic Hernia" as it affects

stomach, diaphragm and neighboring organ function. An excellent series of schematic anatomic drawings adds force to a most unusual and comprehensive group of Roentgenograms. The whole forms the most complete presentation of the subject which it has been our privilege to see. The distinction between *eventration* of the diaphragm and *actual hernia* of the stomach through it or *via* the *hiatus*, admirably is brought out. The surgical significance of true diaphragmatic herniation is emphasized in the light of recent modern opinion; this seems very much worth-while in view of the new types of operation which Truesdale and others have proposed and are performing—apparently with gratifying results.

The surgeon further is kept in mind by the Authors' presenting a complete discussion and a fine sequence of Roentgen reproductions detailing the "Stomach subsequent to operations." Not alone are alterations in gastric function shown but the degree and position of visceral deformities consequent upon the common types of surgery, masterfully are portrayed and commented upon. To the active abdominal surgeon, this section of the work is invaluable—it, alone, warrants the purchase of the volumes.

Volume 2 deals with Roentgen study of the duodenum, in health as well as in disease. The plan of presentation corresponds with that found so admirable in studying the stomach.

Particular emphasis is placed upon discussion of methods where, at the Roentgen study, all segments of the duodenum may be visualized. This chapter is extremely helpful in the study of both the normal and the diseased viscus.

An all-too-frequently neglected aspect of the duodenum and its "bulb," namely, the effects upon position, contour and mobility consequent upon extra-visceral anomalies, here is given very thorough treatment from the Roentgenological and functional angles. The Roentgenograms are superb. The schematic drawings are most illuminating, while the running-text is enlightening and concise. In no work, have we noted so thorough a discussion of the normal duodenum or the artefacts which, if not appreciated, may tend toward the returning of false diagnoses.

After a complete synopsis of the normal duodenum and its "bulb," the subsequent chapters, which discuss and illustrate all forms of functional disturbance and organic lesion of the viscus, most readily are appreciated. It is in this section of the work, *viz*: consideration of the duodenum, that, according to the reviewer's concept, the Authors have excelled even their thoroughly comprehensive presentation of various Roentgen aspects of the stomach. Such pertains not only to the illustrative features but to the unusual quality of the accompanying text. Deformity, due to all types of ulcer, to simple atonic dilatation, to mucosal striations, functional and in association with disease, to stenoses, perioduodenitis, even to malignant disease, most convincingly is demonstrated and discussed.

A unique section well illustrates the possibilities of stenosis at the duodeno-jejunal angle, simple or in conjunction with anomalous mesenteric attachments. Only occasional, scattered references in the literature previously have emphasized this puzzling condition, but Drs. Duval, Roux and Bécélère demonstrate graphically that the anomaly is commoner than has been considered and that when it is present, a confusing picture, clinical as well as Roentgenological, may arise.

Sections dealing with the effects upon the duodenum when disease is present in the gall bladder and biliary tract, malposition or lesions of the papilla of Vater, and diverticula of the duodenum (a lesion which, only recently, has assumed importance, etiologically, Roentgenologically and as a source of dyspeptic disturbances) receive thorough attention, amplified by striking film reproductions and schematic drawings. In no one volume, published in this or other country, have we seen so complete a presentation of either the common or the infrequent lesions in which the duodenum, primarily or secondarily, is involved.

Excellent sections are submitted concerned with duodenal lesions in infants, the effects of para-visceral disease upon duodenal shape, size, contour or position and the disturbances in the function, location and form of the viscus consequent upon surgical procedures. This last section is most useful to internists, surgeons, physiologists and Roentgenologists in appraisal of postoperative anatomical relations and in assisting to explain why, when following successful, mechanical technique, patients yet may exhibit conditions which permit abnormal physiological sequences—secretory or motor.

An adequate, detailed and correct reference index completes the work.

In his early remarks, the reviewer exhibited greater than ordinary enthusiasm for this "Atlas"—its binding, format, text and illustrations. As he became intimately familiar with the work and tested many of the data in specific subjects, he has become increasingly impressed by the uncommon accuracy, the beauty of the illustrations, the wise and judicious use of material, the soundness of the clinical and technical discussions and the immense amount of patience and fidelity which the Authors have brought to their task. The result not alone is a triumph for Drs. Duval, Roux and Bécélère but a tribute to the high quality of work being done in the clinics of France. This reviewer stated some months ago that no American Roentgenologist could consider that his technical and clinical education was complete unless he had visited the teaching, diagnostic and therapeutic actinological laboratories at the University Hospital, Ann Arbor, Michigan. Now he must amplify that statement: most assuredly, no clinician-Roentgenologist in the world can claim completeness in the art and craft of his specialty who has failed to include a *sojourn* in the laboratories of Drs. Duval, Roux and Bécélère. To all such study-trip may be not possible: in that event, one may say that unless the clinician-Roentgenologist's library contains this Atlas newly compiled by our French colleagues, its shelves lack today's most interesting, scientific and useful volumes. To attain this objective should not be particularly difficult in view of the astonishingly low cost of the work (330 francs)—and the rates of exchange all in our favour!

Frank Smithies.

*Textbook of Biochemistry* by Harrow and Sherwin, 797 pages, 52 illustrations, and published by W. B. Saunders Company, Philadelphia and London, 1935.

THE new textbook of biochemistry edited by Harrow and Sherwin has been written by thirty-one American and British biochemists including the editors, who have made original investigations in the field of biochemistry indicated by the chapter each has con-

tributed. This gives each chapter the stamp of authority and assures the reader of the importance and up-to-dateness of the subject matter presented.

The sequence of the chapters is logical. The style is terse, but clear. The method of presentation is remarkably uniform and well-balanced for a textbook written by so many authors. This is due primarily to the conciseness with which the various chapters have been written; in fact each chapter constitutes a brief *résumé* or review of the subject matter in its field. Yet, the book is more comprehensive and descriptive than a synopsis. A conspicuous feature of the book is the absence of biochemical methods or frequently even of a reference thereto. A list of references accompanies each chapter which serves as a satisfactory introduction to the literature. The book contains a bibliographic index of authorities cited in addition to a very completely arranged subject index.

The book was written primarily for students and teachers of medicine whom it will serve well. It will

also serve students and investigators in other fields who desire to add to their perspective concerning the chemistry of biological processes. To appreciate completely the value of certain chapters, the student must possess a thorough knowledge of organic and physical chemistry, i. e. he must know more chemistry than the average medical student. The book will be of value to the gastro-enterologist who desires a more intimate knowledge of the biochemical principles of digestion, nutrition and metabolism, but there is little or no allusion to methods for gastro-intestinal diagnosis and principles of therapy. The gastro-enterologist will find other deficiencies in the book, e. g. the words feces, stool and excreta are not found in the index and their biochemical connotations are not found in the text. There is a good chapter on the chemistry of detoxication which will be of interest to the readers of this Journal.

A. C. Ivy, Northwestern University, Chicago.

## SECTION XI—*Societies, Programs and Proceedings*

### THE FOLLOWING CHANGES IN MEMBERSHIP WERE MADE AT THE ANNUAL MEETING OF THE AMERICAN GASTRO-ENTER- OLOGICAL ASSOCIATION, JUNE, 1935

#### *Advanced from Associate to Active Fellowship:*

Dr. Theodore L. Althausen, University of California Medical School, San Francisco, Cal.

Dr. Everett D. Kiefer, 605 Commonwealth Avenue, Boston, Mass.

Dr. Harry Shay, 265 S. 19th Street, Philadelphia, Pa.

Dr. Edward S. Emery, Jr., 319 Longwood Avenue, Boston, Mass.

Dr. Mandred W. Comfort, Mayo Clinic, Rochester, Minn.

#### *Elected to Active Fellowship:*

Dr. Chauncey W. Dowden, 921 Brown Building, Louisville, Ky.

Dr. Virgil E. Simpson, 321 W. Broadway, Louisville, Ky.

Dr. Carl H. Greene, 889 Lexington Avenue, New York, N. Y.

Dr. Beaumont S. Cornell, 435 Lincoln Bank Tower, Fort Wayne, Ind.

Dr. Clifford J. Barborka, 700 N. Michigan Avenue, Chicago, Ill.

Dr. Adolph Sachs, 525-35 City National Bank Building, Omaha, Nebr.

Dr. L. G. Zervas, Medical School, University of Indiana, Indianapolis, Ind.

#### *Elected to Associate Fellowship:*

Dr. Clarence J. Tidmarsh, Suite 5, 1390 Sherbrooke Street West, Montreal, Canada.

Dr. Edwin L. Gardner, 1629 Medical Arts Building, Minneapolis, Minn.

Dr. David H. Rosenberg, 310 S. Michigan Avenue, Chicago, Ill.

Dr. S. A. Wilkinson, 605 Commonwealth Avenue, Boston, Mass.

Dr. John R. Twiss, 65 E. 55th Street, New York, N. Y.

Dr. L. K. Ferguson, 6390 Drexel Road, Overbrook, Philadelphia, Pa.

#### *Elected to Research Fellowship:*

Dr. Heinrich Necheles, 2900 Ellis Avenue, Chicago, Ill.

#### *Transferred from Active to Senior Fellowship:*

Dr. Dudley D. Roberts, 270 Park Avenue, New York, N. Y.

Dr. Franklin W. White, 322 Marlborough Street, Boston, Mass.

Dr. Seale Harris, 804 Empire Building, Birmingham, Alabama.

#### *Elected to Honorary Membership:*

Dr. Raoul Bensaude, 2, Rue de Penthievre, Paris, France.

#### *Officers of the American Gastro-enterological Association elected at the 39th Annual Session, held at Atlantic City, New Jersey, June, 1935:*

President—Dr. Howard F. Shattuck, New York; First

Vice-President—Dr. Chester M. Jones, Boston; Sec-

ond Vice-President—Dr. Charles G. Heyd, New

York; Treasurer—Dr. A. H. Aaron, Buffalo; Re-

recorder—Dr. Sara M. Jordan, Boston; Secretary—

Dr. Russell S. Boles, Rittenhouse Plaza, Philadelphia.

#### *Members of the Council:*

Dr. Burrill B. Crohn, New York; Dr. Clement R. Jones, Pittsburgh; Dr. B. B. Vincent Lyon, Philadelphia.

#### *Committee on Admissions and Ethics:*

Dr. Ernest H. Gaither, Baltimore; Dr. Irvin Abell, Louisville, Ky.; Dr. Albert F. R. Andresen, Brooklyn.

*Coordination Committee:*

Dr. Burrill B. Crohn, Chairman, 1075 Park Avenue, New York.

Dr. George B. Eusterman, Mayo Clinic, Rochester, Minn.

Dr. Walter L. Palmer, Albert Merritt Billings Memorial Hospital, Chicago, Ill.

Dr. A. C. Ivy, 303 E. Chicago Avenue, Chicago, Ill.

Dr. H. L. Bockus, 250 S. 18th Street, Philadelphia, Pa.

Dr. Chester M. Jones, Massachusetts General Hospital, Boston, Mass.

Dr. Sidney K. Simon, 1520 Aline Street, New Orleans, La.

Russell S. Boles, Philadelphia, Secretary,  
The American Gastro-Enterological Association.

## SECTION XII—"The Clinic"

### A Case of Gastric Polyposis

*By*

A. C. van RAVENSWAAY, M.D.  
ST. LOUIS, MISSOURI

**T**HE presence of multiple polypi in the stomach is of interest from both clinical and roentgenological viewpoints as one of the more important benign lesions of the stomach inasmuch as it may be confused symptomatically and by X-ray with the more common malignant affections. The following case is reported as being representative of this condition.

#### CASE REPORT

A 52 year old, male, negro barber was admitted to Barnes Hospital complaining of epigastric pain and fullness of 5 years' duration, generalized weakness for 4 years, and 20 pounds loss of weight during the preceding year. He had suffered from asthma since childhood. Twelve years previously he had been in the St. Louis City Hospital for 4 months "with his right leg in a cast." Since that time his right hip had been ankylosed.

Analysis of his complaints at the time of admission to Barnes' Hospital revealed that the epigastric pain was increased by food and could be relieved by massage but not by soda. The pain and weakness were becoming progressively worse. There was no nausea or vomiting. Intermittently a hard lump could be palpated in the epigastrium.

Physical examination revealed a poorly nourished, orthopneic, elderly negro man in no acute distress. The ocular fundi showed moderate sclerosis and tortuosity of the retinal vessels. There was marked dental caries. The chest was emphysematous with numerous

rhonchi, more marked on the left. The heart was of normal size; B.P. 110/72. The liver was palpable one finger-breadth below the costal margin. Its edge was regular. In the left epigas-

gms., and W.B.C. 5200. Differential: Eos. 1%, Staubs 4%, Segments 48%, Lym. 36% and Mon. 10%. The sputum contained 2 eosinophils per h.p.f. Stool and urine examinations were negative.

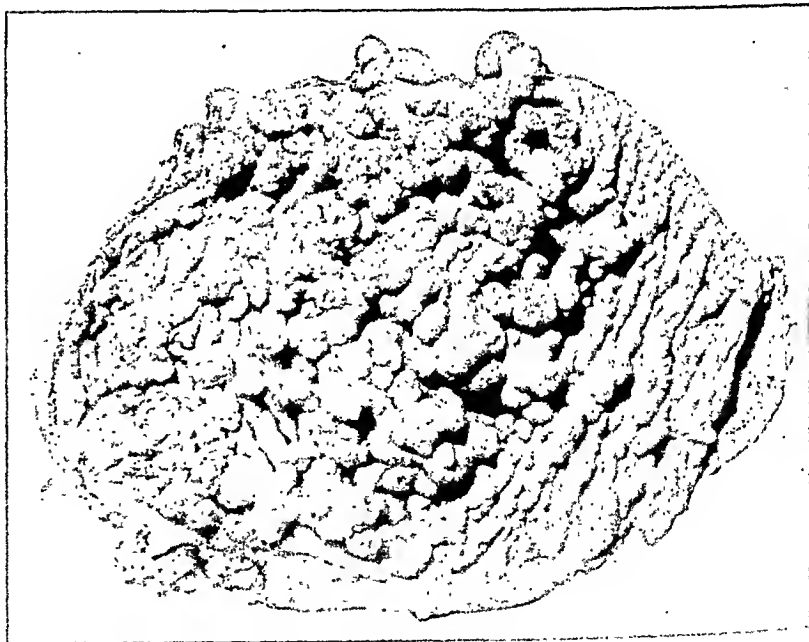


Fig. 1. The stomach after surgical removal. The pylorus may be seen on the extreme right.

trium there was an indefinite mass, tender to deep palpation. The right leg was ankylosed at the hip and was shorter than the left. The toes and fingers were clubbed. The radial arteries were thickened.

**Laboratory Examinations:** The blood study showed R.B.C. 4.07 M., Hgb. 10.7

The gastric contents contained gross blood and there was an achlorhydria.

X-ray examination of the right hip showed healed tuberculosis with fusion. A gastro-intestinal X-ray examination revealed a rapidly emptying stomach, flexible throughout, the location of multiple filling defects scattered through-

\*Mallinkrodt Institute of Radiology and the Department of Medicine, Washington University School of Medicine.  
Submitted March 17, 1935.



cut the entire stomach and most marked on the lesser curvature. The gall bladder did not visualize by oral cholecystograms. The cecum was inverted. The conclusion and diagnosis by Dr. Joseph W. Larimore was diffuse polyposis of the stomach.

At operation on 12-3-34, Dr. Glover Coplier opened the abdomen under intratracheal anaesthesia through a long left rectus incision extending from the costal margin downward. No free fluid was found. The stomach was enormous in size. The serosal surfaces and muscles were not involved. The viscera seemed to be filled with multiple, large mucosal masses, which gave the impression that there was multiple polyposis involving the entire stomach. The liver was free of any pathology. The gall bladder showed chronic cholecystitis without stones. The spleen was of normal size. The duodenum was mobilized, divided, and the proximal end inverted. The entire stomach was removed and the oesophagus was anastomosed to a loop of the jejunum. Because of bleeding, it was necessary to remove the spleen.

On the second postoperative day the patient developed signs of pneumonia at the right base and died in 12 hours.

**Surgical Pathological Examination:** The resected stomach measures 23x14x4 cm., and is distended with dark red blood. Numerous hemorrhagic areas are seen in the mucosa of the cardia. The mucosa everywhere shows a marked polypoid proliferation which is most extensive near the center of the specimen on the greater curvature. The polypi average 2-3 cm. in diameter, and all protrude a similar distance from the mucous membrane. On section, they show a fibrous pedicle and hypertrophied mucous membrane. Microscopical examination gave no evidence of malignant change. Diagnosis: Benign polyposis of the stomach.

#### DISCUSSION

This case exhibits many points of similarity to other reports in the literature and to two other cases of multiple polypi of the stomach previously seen at this hospital. The symptoms usually appear in the late decades of life. They include epigastric discomfort which varies in character from a sense of fullness to severe pain. This may be relieved or accentuated by eating, and is usually not benefited by antacids. Constipation is frequently co-existent. An achlorhydria is almost invariably present and frequently there are signs of bleeding.

At fluoroscopic examination the condition can be recognized by the presence of multiple filling defects in a stomach which organ usually has a soft, flexible wall. If peristalsis can

## ACCEPTED by the AMERICAN MEDICAL ASSOCIATION COMMITTEE ON FOODS



*for the relief of constipation due  
to insufficient "bulk" in meals*

EXHAUSTIVE RESEARCH in leading nutritional laboratories has discovered the scientific facts about bran.

These tests indicate that Kellogg's ALL-BRAN is a natural laxative food for normal people. As a result, this delicious cereal has been accepted by the American Medical Association Committee on Foods.

ALL-BRAN supplies "bulk" to aid regular habits. This "bulk" does not lose its effectiveness when used month after month. ALL-BRAN also furnishes vitamin B and iron, an element of the blood.



The "bulk" in ALL-BRAN is gentle. It does not break down in the body as much as the "bulk" in fruits and vegetables. So it is often more effective.

ALL-BRAN may be used by most people. There are some individuals with diseased or highly sensitive intestines, where "bulk" in any form is inadvisable.

Kellogg's ALL-BRAN may be served as a cereal with milk or cream, or used in cooked dishes.

It is much more effective than part-bran products. Sold by all grocers. Made by Kellogg in Battle Creek.

## The Practice « of Dietetics »

By L. H. Newburgh, M.D.,  
Professor of Clinical Investigation, Medical School  
University of Michigan;  
and Frances Mackinnon,  
A.B., Dietitian, Diet Therapy Clinic, University Hospital, and Instructor, Dept. of Hygiene and Public Health, University of Michigan.

### Comments of reviewers—

"This is a very complete and scientific text and reference book on dietetics. The book will be of greatest value to the physician, the dietitian, and the medical student."

*The Forecast*

"In this book the place of dietetics and diet therapy in medical therapeutics is discussed in a manner that gives the reader a clear picture of its importance, and, at the same time, impresses him with the need for a sane point of view in its practice."

*Practical Home Economics*

"This book contains all the material necessary for the practice of dietetics. It is both didactic and practical. Dr. Newburgh writes as he practices; so direct, clear, and yet scientific that even the student or busy practitioner can understand."

*Long Island Medical Journal*

**\$4.00**

**The Macmillan Company**  
Publishers New York

be induced, it may be observed to pass over the stomach without impairment, indicating the freedom of the musculature from invasion of the pathologic process.

The complications are: interference with digestion and a resultant cachexia; hemorrhage, seldom mas-

sive; malignant degeneration which apparently is much less common in the case of multiple polypi than it is when there is but a single polypus and, occasionally, pyloric obstruction caused by the prolapse of a juxtapyloric polyp into the duodenum.

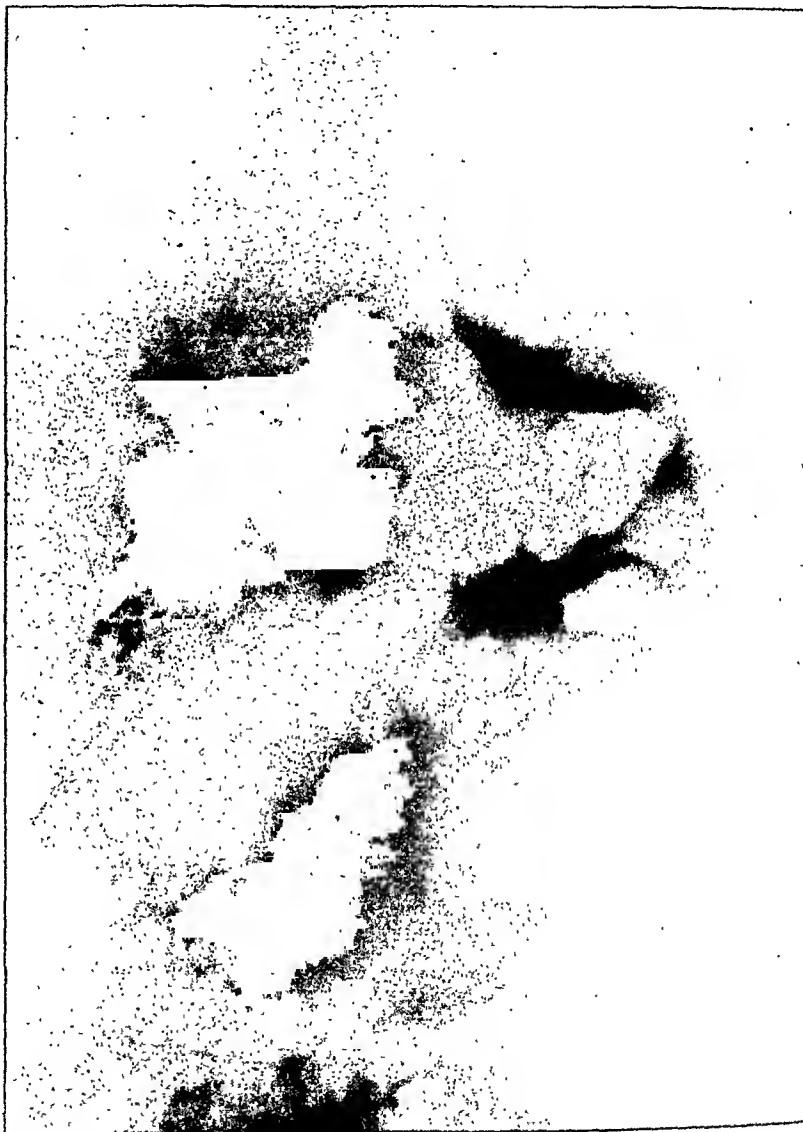


Fig. 2. Antero-posterior view of stomach after the ingestion of two ounces of barium suspended in 70 c.c. of water.

## Non-Tropical Sprue: Report of a Case\*

By

JOHN A. REED, A.B., M.D.  
WASHINGTON, DISTRICT OF COLUMBIA

**S**PRUE ordinarily is considered a tropical disease but is being reported in non-tropical climates

with increasing frequency. Recently Snell, Camp, Watkins (1) made an excellent summary of this disease which report should prove to be a reference *arbeit* for the future. In

\*From the Department of Medicine The George Washington University School of Medicine. Submitted June 1, 1933.

view of the relative rarity of the occurrence of sprue in this country, and paucity of case reports in the literature, I submit an instance and call attention especially to the treatment used which was followed by marked improvement and apparent cure.

# CASE REPORT

Female, age 41, residence, Cumberland, Maryland.

In June, 1933, began to have a diarrhea which became worse following death of her husband in October, 1933. There were 4 to 5 unformed, watery, white, foamy stools a day, each containing soft, mushy, white fecal material. Other symptoms and signs were as follows: marked loss of weight, 33 pounds, stiffness of the joints, swelling of the ankles, weakness, sore tongue, moderate indigestion (gas and belching), fatigability, and capricious appetite. Sleep was only fair.

*Previous history*—no relevant diseases.

*Family history*—of no value will respect present condition.

## Physical Examination:

Drawn, emaciated, depressed appearance. Height 65 inches. Weight 94 pounds. The knee jerks were equal but slightly sluggish, the tongue was coated, the ankles slightly oedematous. The re-

mainder of the physical examination was entirely negative.

## Röntgen Examination:

With the exception of an atonic, redundant type of colon, gastro-intestinal series was normal.

*Wasserman and Kahn*: Negative.

## Fleecs:

Many stools were studied, they appeared putty-colored, frothy but with no microscopic or macroscopic blood or mucus. Abundance of bacteria was present. Moderate amount of undigested starch granules, (Lugol's solution), moderate number of yeast cells, no ova or parasites. Benzidine test faintly positive, guaiac negative; *fat present in large amounts*, (Sudan III stain), occasional fatty acid crystal. *Smear*: negative for tubercle bacilli. *Culture*: plates and subcultures show many usual intestinal non-pathogenic organisms with *B. coli communis* predominating. Special Endo media negative for pathogenic micro-organisms. Tubercle bacillus negative on Petroff's medium and guinea pig injections.

## Gastric Contents:

60 cc. well digested material. Free HCl 14, Total acidity 18. No blood.

*Basal Metabolism Rate*—minus 22%.

*Blood picture*: Sept. 22, 1934. R.C.C. 4,010,000, W.B.C. 500. Hemoglobin 80% (12.8 grams) Smear and differential count normal. November 8, 1934—

R.B.C. 4,130,000, W.B.C. 6800, Hemoglobin 82%.

*Urinalysis*—normal.

*Pancreatic Enzymes* (Dr. Thomas R. Brown, Baltimore, Md.): Diastase 96: trypsin 27.6 mgms. (Normal).

## DISCUSSION

It is interesting to note that after 27 examinations and two consultations, diagnostic impressions only were reached and treatment was instituted somewhat empirically. Such cases of steatorrhea are so uncommon in the private practice of gastroenterology that they are apt to be undiagnosed or incorrectly so.

After fair exclusion of tuberculosis and disturbed fat metabolism, a typical or non-tropical sprue was considered and treatment instituted towards its alleviation.

Various forms of management had been used in the cases reported with no improvement. A diet with little or no fat was given and liver extract intramuscularly was started. The protein content was fairly high. Calcium as calcium lactate together with hydrochloric acid and haliver oil and viosterol were administered. Four days afterwards the white watery foamy stools disappeared replaced by

## TILDEN has Kept Faith with Physicians

### MALTO-FERRO (TILDEN)

- **C**ONSISTS of Iron Ammonium Citrate, 80 grs. per fluid ounce, Hypophosphites, Extract of Cod Liver Oil, Malt, and other ingredients, combined in a manner exclusive with Tilden.
- MALTO-FERRO (Tilden) has been prescribed for secondary anemias and general debility, conditions of the system manifesting subnormality in metabolism. The large dose of Iron and other reconstructives is absorbed rapidly, and the blood deficiencies corrected, without gastric upset or constipation.
- Symptoms of nervousness, insomnia, constipation, loss of appetite and weight, yield readily to prescriptions of MALTO-FERRO.
- MALTO-FERRO (Tilden), like all prescription specialties produced by The Tilden Company, is labeled according to law, advertised only to the medical profession, manufactured under strict scientific control, and offered only after years of thorough clinical success.

Literature will be furnished confidentially to physicians only on request.



AJD 8-35

## THE TILDEN COMPANY

The Oldest Pharmaceutical House in America

New Lebanon, N. Y.

St. Louis Mo.

a soft, unformed, brown, mushy movement. In 10 days' time, normal sausage shaped stools were noted and many of the symptoms had disappeared. About 3 weeks after management had been instituted, the patient went on "a dietary spree" which resulted immediately in a return of the white foamy watery stools. She immediately returned to the "fat free" diet and in two days improvement was noted. Since November past, gain of weight has been steady so that her present weight is 131, a total gain of 34 pounds with subjective complete recovery.

### SUMMARY

A case diagnosed as non-tropical sprue is presented because of the relative rarity of the affection. Authors previously mentioned state that something over a hundred cases are now on record. The treatment suggested, while by no means original, was efficacious.

### REFERENCE

1. Snell, A. M.; Camp, J. D., and Watkins, C. H.: *Proced. Staff Meet. Mayo Clinic*, Vol. X, page 178, March 20, 1935.

Accept this box of 18  
tablets, Doctor,

then make your own clinical test of

**TAUROCOL**

(TOROCOL)

**Bile Salts Tablets**

Taurol increases motility, increases peristalsis and steps up the flow of bile by stimulating the bile producing cells of the liver.



SEND  
COUPON  
TODAY

THE PAUL PLESSNER CO., J.D.F-35  
3533 Brooklyn Ave., Detroit, Mich.

Yes, please send samples.

M.D.

Name of Doctor

## ABSTRACTS

SAMUEL MORRISON, M.D., AND MAURICE  
FELDMAN, M.D.

*The Effect of Bacteria on the Normal Stomach and on Acute Experimental Gastric Ulcer in Dogs. Am. Jour. Med. Sc., Vol. 189, No. 5, May, 1935.*

Experimental work of the authors deals with the effect of bacteria upon the normal gastric mucosa and with the mucosa of acute ulceration produced by hydrochloric acid.

It was found that large amounts of bacteria mixed with food did not produce ulceration when fed to the dogs. When bacteria were fed to the animals in which acute ulcers had been produced by hydrochloric acid, no infection of the ulcer took place, the ulcer healing completely.

The administration of sodium bicarbonate did not produce any effect upon the gastric mucosa or ulcers.

The investigators injected potent cultures of bacteria into the gastric wall usually without the formation of abscess or necrosis.

The authors concluded that the acute hydrochloric acid ulcer is clean-cut, non-infected, and apparently does not lend itself to bacterial infection. Some other factor must play an important role in the production of chronic ulcer.

H. W. Soper, St. Louis.

ALVAREZ, WALTER C., AND HINSHAW,  
H. CORWIN.

*Foods That Disagree With People. J. A. M. A., 104:2053, June 8, 1935.*

Five hundred patients of fair or good intelligence who were complaining of indigestion, were questioned about foods that they could not eat or could only digest with discomfort. Onions, apples,

cabbage, milk, chocolate, radishes, tomatoes, cucumbers, eggs, fats, cantaloupe, beef, strawberries, coffee, lettuce, dried beans, cauliflower, melons, pork, corn, and pickles were common offending foods.

A number of patients with migraine incriminated certain foods in connection with their headaches. Among the foods were chocolate, onions, milk, peanuts, cabbage, and eggs.

Transient urticarias were commonly ascribed to the following foods: Strawberries, tomatoes, eggs, fish, milk, and chocolate.

Foods that are seldom mentioned by patients with indigestion as having any bearing on their discomfort are lamb, gelatin, butter, sugar, rice, rye, barley, arrowroot, tapioca, sago, lima or soy or string beans, cooked apple, pineapple juice, beets, asparagus, peas, Irish or sweet potatoes, egg plant, turnips, parsnips, pumpkin, artichokes, cooked pears and weak tea. These foods can be used as a basis for elimination diets.

The authors stress that the digestibility of foods has received but scant attention, that food sensitivity is not all on an allergic basis; that each individual must be studied as to his dietary requirements, and that ready-made diet lists and general instructions against fried or greasy foods are inadequate.

Francis D. Murphy, Milwaukee.

Error: In the July issue, on page 330, in the article by Dr. George B. Dorff, on "An Instance of Marked Abdominal Distension," the two half tones showing the colon should be interchanged to suit the present legends.

### SUBSCRIPTION BLANK

American Journal of Digestive Diseases and Nutrition  
435-455 Lincoln Bank Tower,  
Fort Wayne, Indiana.

Enclosed please find \$6.00 (Foreign \$7.00) for one year's subscription to the American Journal of Digestive Diseases and Nutrition.

Name .....

Street .....

City ..... State .....

# SECTION I—*Clinical Medicine: Diseases of Digestion*

## A Philosophic, Clinical and Retrospective Discussion of Certain Major Problems in the Digestive Field\*

By

THOMAS R. BROWN, M.D.  
BALTIMORE, MARYLAND

DIGESTION dates back to the beginning of life, to the primitive needs of the first unicellular organism in the primordial ooze. It has been worshiped and deified; it has been damned and its followers reviled in the high places. But it is neither god nor devil, for no god would endure the insults to which it is subjected from the cradle to the grave; no devil would fail to utilize to the full the almost hourly opportunities to raise its dysfunction into consciousness. In reality it is a faithful, willing, hard working beast of burden, doing its best to carry on under an ever-increasing load. To lessen this load, to make the burden lighter, many men in many lands have striven mightily and not altogether in vain. Knowledge has come from many sources, from the chemist and physicist with their newer ideas of molecular structure and their better knowledge of the chemistry of digestion; from the physiologist and the pharmacologist, test tube in one hand, guinea pig in the other; from the pathologist, the surgeon and even from the clinician.

We are still ignorant of much for, as Chaucer quaintly sings—

*"The Lyfe so short;  
The craft so long to learn."*

But we do know a little and with this knowledge and with what experience has taught me from many years in general medicine, in not a few of which this special field has had my major interest, may we journey together through the digestive tract with a few side trips into certain of its backwaters and estuaries.

I will speak only from my own experience, rarely quoting from others, and while there will be many moot questions brought up and some where much controversy lies, at least you will know at the end of the voyage what I have learned to believe and disbelieve, what has helped me and what has not, what I have discarded and to what I have clung in this *voyage digestif*.

First the *oesophagus*, then a few side trips into the realm of referred symptoms from heart, from lungs, from renal and genital apparatus; then touching upon the major problems below the diaphragm—carcinoma, ulcer, pancreatic and biliary disease and diseases of

the intestine; a trip that must perforce be very rapid but which I hope will not be entirely devoid of interest.

*Mouth:* It is needless to state that before leaving port it is essential that we be sure its superstructure is in good order. Unquestionably far too much stress has been laid upon teeth and tonsils as foci of infection in disease elsewhere. Thousands of teeth and tonsils have been extracted for a vast variety of pathological conditions, which were not in the least benefited by such treatment. Now, when we recommend such procedures it is in the spirit of humility,—tempered hope in the place of blind faith. Nevertheless, irrespective of what rôle the mouth plays in disease elsewhere, it is wise to have a clean mouth, with good teeth and plenty of them, so that the complicated process which we call digestion and metabolism may have a fair start.

*Oesophagus:* The functions of the oesophagus are so simple that its problems are few, but these few are interesting, especially new growth and so-called cardio-spasm, better termed "oesophagospasm," as the constriction, as a rule, does not occur at the cardia but just above it where the gullet passes through the diaphragm. Is this a true neurosis? I have seen certain cases following immediately upon profound shock which would suggest it. Is it reflex in origin from elsewhere—appendix, gall bladder, marked visceroptosis? Is it due to degenerative changes in the plexus of Auerbach or Meissner at the lower end of the tube? Is it really not oesophageal but diaphragmatic in origin, and if extremely severe, should phrenicotomy be considered, and would it help? Is it really not a spasm but an absence of normal relaxation—an achalasia?

Most of these are considered in our therapy—sedatives, psychotherapy, a smooth diet, anti-spasmodics and lubricants, perhaps operative treatment on appendix or gall bladder if diseased, an attempt to put on weight in high grades of visceroptosis, but these forms of treatment are often very disappointing. At the present time in many cases a series of dilatations, repeated at varying intervals, is the only thing that will bring about relief until some better method of attack is discovered.

As regards cancer of the oesophagus, its diagnosis is usually easy. The progressive, occasionally intermittent dysphagia of the old should always arouse sus-

\*From the Division of Digestive Diseases, the Johns Hopkins Hospital and Dispensary.  
Submitted July 5, 1935.

picion and radiological studies, oesophagoscopy and biopsy should give us our diagnosis. These cases should be diagnosed early; they metastasize late. Like almost all the digestive neoplasms, with the possible exception of colloid growths, they are not ray sensitive and in my experience ray therapy has been extremely disappointing. Therefore, while their symptoms may be ameliorated by dilatation or gastrostomy, cure is only possible by radical surgical procedures. So far these have been disappointing in the extreme, but I firmly believe that with the tremendous strides in chest surgery, a successful technic will be found, possibly, as Rienhoff has suggested, by decompression of the lung, the production of a diaphragmatic hernia, and the anastomosis between the upper end of the oesophagus and the stomach well up in the thorax; thus minimizing excessive traction on the oesophagus, which is met with in other operations and which makes the anastomosis breakdown and death come from mediastinal infection and pneumonia.

*Referred Symptoms:* And now before we leave land and sail away below the diaphragm, may we take a short side trip into other nearby channels, all having one thing in common, their ability to project the symptoms of their pathology into the digestive sphere. The whole question of referred symptoms is a fascinating one. Its basis of course is the peculiar innervation of the abdominal and thoracic viscera, their double nerve supply; an autonomic system made up of two sets of essentially antagonistic fibres, sympathetic and parasympathetic, and the practical lack of pain fibres; that is, a mechanism which renders exact localization difficult or impossible. While this is the major factor in most referred symptoms, one must not forget that these may also be brought about by other conditions, such as proximity of certain organs. For instance, the diaphragm is all that separates heart and lungs from stomach and upper abdominal viscera; while both the genital and urinary apparatuses are in such close proximity to appendix and to colon and their nerve supply so intimately and intricately interrelated, that it is no wonder that the symptoms in either field may extend into the other.

One other factor, the chemical, must not be forgotten—the effect of the products of disease, toxins, normal substances in excessive amounts or the abnormal products of disease, which for some inexplicable reason select some special organ or tissue for their major manifestations. For example, the acute abdomen of diabetic ketosis, the appendicitis-like picture of certain of the infections—measles, influenza, typhoid, rheumatic and undulant fevers—the simulation of carcinoma of the stomach by certain cases of chronic interstitial nephritis, for its achylia, anorexia, loss of weight and tendency to mucosal hemorrhage sometimes present a very puzzling picture; the functional dyspepsia of early tuberculosis, the chronic constipation of certain of the often unrecognized cases of hypothyroidism, the diarrhoea met with occasionally as the earliest symptom of the overactive thyroid and the number of extra gastro-intestinal conditions associated with achlorhydria or true achylia, sometimes with, often without, digestive symptoms, such as pernicious anemia, the arthritides, both infectious and metabolic, chronic cardiorenal disease, sprue and pellagra, disease of the gall bladder and after a certain number of cholecystectomies. Finally the emotions whose reper-

cussions upon the digestive sphere play the major rôle in that enormous field so difficult to treat successfully—the so-called digestive neuroses.

I have been singularly interested for many years in the inter-relation of cardiac and gall bladder disease; not the well known increased incidence of gallstones in cardiopaths or the fact that certain cases of myocarditis seem to be due to chronic biliary tract infection, but certain rarer associations, as for example coronary thrombosis, with symptoms so entirely below the diaphragm, and so closely resembling acute gall bladder disease that operation has been performed on that assumption, and the even rarer cases of unsuspected gall bladder disease usually associated with stone, where we may have as the only symptoms the almost classical syndrome of stenocardia or coronary thrombosis or the failing heart. Here, if we get but a clue to justify it, cholecystectomy may make the cardiac picture clear up as if by magic. Perhaps the production of anoxemia by rebreathing may help us to decide what is the fundamental pathology in these two groups of cases.

The first signs of a failing heart may be a simple banal dyspepsia, presumably due to a passive congestion manifesting itself first in this viscus. Here digitalis will succeed when diet and other drugs have sadly failed. Of more than passing interest are the extremely rare cases of rapidly dilating heart with intense upper abdominal pain, possibly due to sudden stretching of the capsule of liver and spleen; while rupture of the heart may have only abdominal symptoms.

In the case of the lungs, the most interesting examples of referred symptoms are those of the acute abdomen usually simulating appendicitis or intestinal obstruction, met with in certain cases of central pneumonia or diaphragmatic pleurisy, while I have been much interested in the atonic dyspeptic picture seen after certain phrenicotomies in tuberculosis. Incidentally it is worth remembering that in almost a quarter of the cases of pulmonary tuberculosis, the earliest symptoms are not pulmonary but digestive. Early pregnancy may often be undiagnosed and treated as a gastric neurosis; it is not unusual for a retroflexed uterus in a neurotic girl to have severe digestive symptoms, usually anorexia or intractable vomiting; while of course we all know how often salpingitis, an ovarian cyst with twisted pedicle or a ruptured extrauterine pregnancy is mistaken for an acute appendicitis.

The gastro-intestinal symptoms in diseases of the urinary tract are met with with great frequency. A renal calculus or a true ureteral stricture or a floating kidney may simulate peptic ulcer, gall bladder disease, colitis or appendicitis. An acute or subacute right-sided pyelitis so common in children, especially in girls, may be very difficult to differentiate from appendicitis, especially as the urine may be clear for some little time due to the plugging of the ureter on the affected side.

Finally there is that great number of digestive symptoms met with in organic and functional disease of the central nervous system. Hysteria simulating anything and everything; the crises of tabes giving us a picture of ulcer or gall bladder disease, sometimes even leading to operation—an unpardonable error for a complete physical examination will practically always



give us our diagnosis—the digestive aura of epilepsy, migraine and Meniere's disease.

Verily to sail this sea safely one must be no mere specialist, but must know something of every other path as well, if one hopes successfully to solve these puzzles; to unravel the tangled skein of organic and functional disease with their myriad manifestations and to interpret the significance of abdominal pain.

*Cancer:* And now, back again to the main channel. Of course the most important disease in the digestive tract is cancer. It causes more deaths than cancer of any other system. It has been known since the beginning of recorded time. It is mentioned in the Rig Veda and Eber's papyrus. It seems to be definitely on the increase, but whether this is due to better methods of diagnosis, and to greater longevity or whether it is real and due to something in our modern civilization—mental strain, new forms of trauma, or the modern diet—one cannot say. It is singularly insensitive to all forms of ray therapy, to colloid metals or to lead; there is but one potentially effective treatment—surgery. To increase the percentage of cures by operative treatment, early, or relatively early, diagnosis is necessary, relatively early, alas, because in many cases, especially in growths in the "silent" area—the lesser curvature of the stomach—there may be a long symptom-free period and what we think is the first or second, is, in reality, the third or fourth act of the drama. The life cycle of gastric carcinoma and, to a lesser extent of intestinal carcinoma, must be often much longer than usually supposed—two to four years instead of six months to one year.

We know something, but very little about the cause of cancer. There are certain agents which in the laboratory or in clinical experience frequently seem to produce the disease; parasitic infection as in the cancer of rats—due to *spiroptera neoplastica*; chemical and physical agents such as tar, oils, exposure to various rays, sun, X-ray, radium—incidentally a step forward has been taken in the case of chemical irritants by the demonstration that the carcinogenic substance in tar corresponds closely to compounds of the Dibenz anthracene series—and finally the virus of the filterable tumors of birds. Heredity unquestionably plays a rôle in certain cases, probably as a Mendelian recessive.

But the fundamental question is: is there some unknown underlying mechanism common to all? In other words, is cancer one disease or several? In some cases, the embryonal rests of Conheim seem to offer a perfect explanation, in other cases the theory is hard to accept. Not knowing the cause, how then can we make an early diagnosis in carcinoma of the stomach or intestine? There is but one answer—the careful analysis of the patient's symptoms, however slight, however commonplace, if they appear in middle or later life, if they appear without cause and if they do not yield to the ordinary therapy based upon the idea that they represent a functional disorder. In the stomach, this is usually a simple, banal dyspepsia without pain; in the small intestine, relatively few or no digestive symptoms. But fortunately neoplasms here only represent a little over one-half of one per cent of the total cases of digestive new growths; in the colon, progressive or intermittent constipation, occasionally alternating with diarrhoea, or attacks of colic, almost always diagnosed as "nervous indigestion" or "mucous colitis."

But through it all—the one common finding—the symptoms come out of the blue as a thief in the night, usually with no previous history of indigestion and not yielding to symptomatic treatment. Intensive diagnostic methods—X-ray plates and fluoroscopic examination, digital rectal examination and sigmoidoscopic study, study of the stool for occult blood, gastric analysis, palpation in the hot bath, all will add to our knowledge and may give us our diagnosis, but without the primary suspicion such studies would never be inaugurated.

In our experience as regards the stomach, an ulcer syndrome or symptoms of a subacid or achylic gastritis have been present in only a small percentage of the cases—about 15% in our series. About 85% of cancers appear spontaneously without evidence of previous gastric disease or dysfunction.

While the general principle that success of surgery depends on the relative earliness of the diagnosis is a sound assumption, it is well to remember that the size of the growth and its operability are not always necessarily associated. Some of our most successful cases have been in extremely large, palpable tumors, while in certain other cases, the original growth may be extremely small, but its metastases extensive and apparently early.

What are the results of surgical treatment so far? Not too encouraging as yet. Our series gives considerably lower figures of relief than the reports from the Mayo Clinic; but 18% of the gastric cases operated upon lived approximately two years or more; about one-eighth over five years; while in growths of the colon our results, while again not so good as Rankin's, are far from discouraging.

Frankly, I would far rather advise operation on a well grounded suspicion than to wait until a definite diagnosis can be made, but where as a rule surgical removal is impossible. Delay means simply that a condition potentially responsive to treatment in its early stage has become so extensive or so disseminated that radical removal is impossible.

*Peptic Ulcer:* And now to the great battlefield of the abdomen—peptic ulcer—its cause, its diagnosis, its treatment! I have often wondered if Cruveilhier does not stir uneasily in his grave when he realizes the century of conflict that has followed in the wake of his epoch-making description—between surgeon and clinician; between the proponents of the many types of diet and operation suggested; and between the champions of the so-called specific methods of treatment.

*"Each champion to the other's virtue  
blind  
And thinks his treatment only cures  
mankind."*

And yet, *mirabile dictu*, all claim practically the same percentage of cures—75 to 80%; in all the same time, between three to six weeks, to bring about a cure. All seem to have forgotten that uncomplicated ulcer is a self-limited disease and only the most pernicious forms of therapy will prevent it from healing in its self-appointed time. Certain simple rules should of course be followed. The diet should be non-irritating, of high caloric value, non-stimulating to acid secretion, capable of combining with hydrochloric acid in considerable amounts, the meals at relatively frequent intervals; this is all! If unnecessarily restricted, it may lead to marked malnutrition and very occasion-

ally a pellagra-like picture. Personally I feel that hourly feedings are absurd. They are a great hardship to the patient and to the nurse and utterly unnecessary, as I am convinced that the ulcer heals better in a low acid than in an alkaline medium as Bolton showed so beautifully in his experimental work. Rest is essential, but not necessarily physical rest; mental placidity is far more important and this is often better brought about by ambulatory treatment, especially if there is an economic factor, than by hospitalization.

I am certain recurrence of ulcer comes much more frequently from psychic than from physical trauma. We do not know the cause of ulcer, we do not understand the *rationale* of its characteristic pain, nor why the mucous membrane is sensitive, at certain times, to stimuli to which it is insensitive at other times. But barring complications, the great problem in the treatment of ulcer is not really the cure, but the *aftercure*. How to make the patient for weeks, for months, even for years, follow the proper regime—psychic, hygienic, dietetic, possibly medicinal—that reduces to a minimum the chance of recurrence. This is not so much a question of the knowledge as of the personality of the doctor.

Hydrochloric acid is of course essential in the production of ulcer—Mann's and Williamson's experiments have shown this beautifully, but this is a far cry to saying that hyperchlorhydria is the primary cause of ulcer.

What is this primary cause? Is it infection or trauma, congenital tendency with characteristic body form? Is it allergy or lack of certain vitamins? Is it vagal-sympathetic imbalance? Is it of reflex origin from appendix or gall bladder? Is it of psychic or endocrine origin? Is it due to local vascular disease or disturbance? Is it brought about by heteropic intestinal mucosa or is it due to an insufficiency of neutralizing alkaline duodenal secretion? Does omental infection or adrenal dysfunction play a part? Is it in reality a secondary condition to a preceding gastritis or duodenitis—a very popular view at present among the German investigators? Experimental work does not answer these questions for ulcers produced in animals by a variety of agents are not like the peptic ulcer of man in their behaviour. Until we know the primary cause of ulcer, if there be such a primary cause, prevention is difficult and treatment often unsatisfactory and symptomatic. After all, in the treatment of most digestive diseases it is not so much the pathological process itself as its associated functional disturbance that we must attack if we hope to get relief. For instance, nothing is of more interest than the unraveling of what seems to be a high grade pyloric or duodenal obstruction, to determine—how much is due to organic change, how much to oedema and inflammation, and how much to associated spasm? In this condition always try rest, a soft diet and submaximal doses of belladonna before advising surgery.

Unquestionably the tendency is more and more towards treating ulcer by medical, physical and dietetic, rather than by surgical means, but of course certain conditions such as true marked organic obstruction, deforming adhesions preventing normal physiological function, repeated hemorrhage probability of malignant degeneration and of course perforation, require operative treatment. As in every other form of abdominal disease, however, it is a wise thing to re-

member that the more clearcut the diagnosis, the more definite the need—the more successful will be the result of surgery. Gastroenterostomy does not stop hemorrhage, but it does help immensely in the obstructive cases. Large resections seem to me unjustifiable. Pyloroplasty is often technically impossible and few can do it well. Gastroduodenostomy or small resections would seem to me often the best operation especially in the non-obstructed group. But there is not, and probably never will be, an ideal operation for ulcer. Each has its defects but each, to make the chance of its success greatest, must have the proper preoperative and long post-operative care.

*Gall Bladder:* And now to that other great field of conflict, the gall bladder—alas, also a land of flux with doubt as to etiology, correct diagnosis and proper treatment. We probably operated upon too few gall bladders before cholecystography; we certainly operate upon far too many since it has become almost a routine diagnostic procedure. Here, as in the case of ulcer, the best results are always obtained where the history is clearcut and where the cholecystographic picture shows stones or very gross deformity; the greatest proportion of failures where the history is vague, the surgical indication is not definite, and the X-ray study shows either no shadow or faint shadow and delayed emptying. In the former group, the percentage of cures is probably over 90; in the latter group, the percentage of failures is extremely high, 40 in Graham's series, over 50 in ours.

Rous has shown us that in the dog, the concentrating power of the gall bladder varies from three to elevenfold; it is probably the same in man, and therefore variations in density should not be taken too seriously; while lack of filling may be of intestinal rather than of hepato-biliary origin.

We have found from a careful analysis of all of our cases that there is an error of approximately 20%, both positive and negative, in cholecystograms as shown by the subsequent history of the case. This, incidentally, is not much less than if the diagnosis were made from a careful history of the case, through physical examination and the utilization of the usual laboratory studies by a competent clinician.

I am sure that it is wrong to consider the gall bladder as a separate entity and not as a part of the entire biliary tree, although in a considerable proportion of cases, the major portion of the pathology is concentrated there. It is in this latter group where surgical attack upon the gall bladder is likely to be most successful. I am convinced that, in analyzing the symptoms, we must determine how many are referable to the gall bladder itself, how many to liver, ducts and biliary tract, for on the results of such analysis, must rest our decision as to medical or surgical treatment; and, if the latter is decided upon, what is the best operative procedure.

I am quite sure that cholecystectomy is the operation of choice in the vast majority of cases in which surgery is indicated, and, that in a good many of these cases, complete relief may be obtained by the removal of the gall bladder. I am equally convinced that where there is evidence of extensive liver and biliary tract infection as well, it is far wiser, if surgery is to be done, to employ cholecystostomy, possibly followed later by cholecystectomy; or cholecystgastrostomy.

It is true that cholecystgastrostomy and cholecystoduodenostomy have their dangers in possible ascend-

ing infection, but it is the lesser evil. Quite frankly, when I am convinced that hepatitis and intrahepatic biliary tract infection are playing a large rôle in the picture, even with the knowledge that the removal of the gall bladder usually brings about a compensatory dilatation of the entire biliary tree, I am loathe to suggest cholecystectomy and often advise one of the operations which promotes constant drainage because the more radical operation takes away a crutch upon which later we may want to lean.

Even cholecystectomy has its dangers and disappointments. I have had recently two patients in hospital who have had to be operated upon for gross pyloric obstruction secondary to extensive post operative adhesions following this operation, while I see a number of cases where partial post operative common duct obstruction is met with due to this same cause.

To learn most about the problems of gall bladder disease and ulcer it is essential that the clinician should be present at the operative cases if the treatment be surgical. He will learn a little from his successes and a great deal from his mistakes. He may even sometimes aid the surgeon a bit in his choice of the proper operative procedure.

Our newer knowledge of gall bladder and biliary tract pathology should be tremendously helpful to us in the medical handling of these cases and there are more and more cases which we are trying to relieve if not cure by non-surgical means. Our debt to the physiologists, notably Ivy and Mann, is very great. We know something of the rhythmic tonus and the tonic contractions of the gall bladder, and of the function of the sphincter of Oddi. It has been shown that the gall bladder itself can contract and incidentally, if associated with a simultaneous contraction of the sphincter of Oddi and the duodenal musculature may produce a picture exactly simulating gallstone colic.

We know the hormone which brings about the normal mechanism, "cholecystokinine," and that fats, especially egg yolk, and to a lesser extent olive oil and butter liberate this perhaps better than anything else. We know the effect of bile salts, dihydrocholic acid and various salines, notably the magnesium salts, on the elimination of bile. From this knowledge we can plan a scientific treatment which is often surprisingly successful in a number of these cases: A smooth diet with plenty of the proper fats, frequent feedings, a saline in the morning or before meals, the clearing up of upper respiratory and mouth infections, the avoidance of constipation, the use of various substances to increase bile elimination, possibly antispasmodics and the proper use of exercise and rest, mental and physical.

As in the case of ulcer, the proper balance between non-surgical and surgical attack is being better and better established.

**Pancreas:** No organs play a larger role in digestion and absorption than pancreas and small intestine, but in no organs are their minor diseases and dysfunctions less well understood. Carcinoma of the pancreas with its progressive painless jaundice, sometimes, however, almost exactly simulated by painless common duct stone or pancreatic cirrhosis; acute hemorrhagic pancreatitis, with its striking picture of circulatory collapse, and cysts of the pancreas are practically all of the conditions we diagnose. And yet there must be innumerable cases of subacute or chronic pancreatitis, usually associated with gall bladder disease, and of functional disturbances which are never suspected.

I am quite sure that many of the vague upper abdominal syndromes met with in the old, usually associated with slight rather vague pains, are of this origin. Certain of the diarrhoeas with excessive fat in the stool, I believe are due to functional pancreatic disturbance, while I am convinced that in certain cases of sprue a pancreatic hyposecretion is associated with the intestinal hyposecretion and muscular hypotonus so characteristic of this disease and that in these cases pancreatin is a helpful adjuvant to liver and other forms of therapy.

Certain cases of carcinoma of the pancreas or even cases of chronic pancreatitis—conditions sometimes extremely difficult to differentiate from each other even at operation—may closely simulate cancer of the colon, a point, incidentally, insisted upon by Dr. Halstead. In all of these pancreatic problems, carcinoma, pancreatitis, functional disturbances, I believe quantitative and qualitative ferment estimations from duodenal contents or stool may prove of real help in many instances.

**Small Intestine:** The small intestine—that laboratory where digestion and absorption go hand in hand—is still a land of mystery. We can learn little from X-ray or laboratory studies. It is almost impossible to estimate its fermentative powers. We have no test by which to gauge its absorptive powers. Now and then by repeated fluoroscopic studies we are able to diagnose or suspect a neoplasm; occasionally we can recognize the rare localized tuberculosis of the intestine, a quite different picture of course from the terminal diffuse tuberculous enterocolitis almost invariably present in the final stages of pulmonary tuberculosis.

The veil is lifted a bit by our study of celiac disease in children, of sprue and sprue-like disorders in the adult. We know that in these cases, fats are badly borne, but, in addition, that the higher molecular fats such as meat fats and those having a higher degree of saturation, are far less well absorbed than the lower molecular unsaturated fats such as olive oil; that the monosaccharides are well borne, the disaccharides and polysaccharides often not well borne.

We do not understand why bananas help certain of these cases. It does not seem due to any ferment which they contain. It may be due to their high content in invert sugars or to the softness of their cellulose; possibly they contain an essential principle. But it is an undeniable fact that in this group of cases a diet of protein, egg white, skimmed milk, minced liver, etc., with marked restriction of animal fats, di and polysaccharides, and with a large amount of monosaccharides, olive oil and bananas, will prove extremely beneficial.

Finally, what is the cause of that peculiar inability to take care of carbohydrates—not fats—met with in intestinal carbohydrate indigestion, the so-called "fermentative dyspepsia" of Schmidt, with its large yellow acid stools, showing many starch granules, but where fat and protein are both well digested? It is probably not pancreatogenous. We have found normal pancreatic diastase readings in all of these cases. It seems to be one of those complex intestinal problems, where both deficient digestion and deficient absorption play a rôle and where the only really successful treatment is a long period of protein-fat diet.

**Appendix:** Only a moment's stop in the lower right quadrant. Is there such a thing as "chronic appendi-

citis" with no history of acute attacks, sometimes with local but more often with referred symptoms elsewhere, especially in the epigastric region simulating ulcer? I believe so, though many of my surgical friends disagree, for although the diagnosis is unquestionably incorrect in the vast majority of cases and surgery almost always unsuccessful and disappointing; nevertheless I am sure that there are a few cases where the condition is present, where the symptoms are due to the condition and where the removal of the appendix gives brilliant results.

I have been helped in diagnosing this small group by multiple fluoroscopic studies, before and after purgation; by palpating the appendix is visualized under the fluoroscope and attempting to reproduce the symptoms, and by repeated study of the leucocytes and the temperature readings. In acute appendicitis, as in every other acute abdominal condition, until the diagnosis is made and the treatment planned, there is no safer rule than this—absolute rest, complete starvation, no medication.

*Colitis:* The next step in our voyage is one that I approach with a great deal of trepidation. The colon is worshipped by many as the cause of multitudinous diseases elsewhere but I, alas, am not among its worshippers, nor am I blinded by its new effulgence. Perhaps the most interesting problems in regard to it are its bacteriology, its rôle as a focus of infection and the many problems connected with ulcerative colitis.

It is worth remembering that years ago Cushing and Livingood showed that the ileum usually contains a preponderant number of streptococci, that Garrod later found that by active purgation the normal streptococcal content in the rectal stool of from 1% to 2% can be raised to 30% or more; that Lyons in England demonstrated that in the bits of mucus in the stool in colitis, many more streptococci could be found than in the fecal mass; while Paulson in my Clinic has shown that blood as met with in ulcerative colitis is the perfect culture medium for streptococci and incidentally for certain other organisms rarely found in the intestine—*pyocyaneus*, *proteus* and Frielander's bacilli—while it markedly inhibits the growth of the usual colonic flora, especially the colon bacilli.

From our Clinic, Paulson has also shown that in the normal intestine, at various levels, one can obtain every micro-organism to which has been ascribed pathogenic properties, including the gram positive diplococci, which some have regarded as the cause of so-called "non specific ulcerative colitis."

Incidentally I am still ignorant of the cause of this condition. I am not sure it is primarily an infection and that it may not represent changes in the mucosa or gut wall which lower their resistance to infection. I do not believe it is responsive to so-called "specific therapy," nor that in the vast majority of cases it is an aftermath of bacillary dysentery. I cannot accept any specific micro-organism as its cause and I still think that general hygiene, a high caloric, low residue diet, rest, good care and upbuilding treatment are the main factors in its treatment. Non-specific protein therapy sometimes gives relief, but it is not curative. Irrigations, I think, are fundamentally unsound, and probably do more harm than good in many cases.

I believe that many apparent successes under so-called "specific cures" are simply expressions of the natural remission peculiar to the disease. I am sure

rest of the gut is the great *desideratum* and I feel that if operation is necessary, the best is that which gives the maximum quietude to the diseased gut, ileostomy if the entire large bowel is affected; colostomy if the ulceration is confined to sigmoid and rectum as it is in a certain proportion of cases.

In regard to the so-called "*mucous colitis*," I feel that the irritable colon may be purely psychogenic in origin and in its earlier phases best treated by re-education and psychotherapy, though not always successfully as many cases represent a true congenital autonomic imbalance, where certain drugs, especially belladonna, will have to be used as well. On the other hand, when that stage is reached, when mucus is found in large amounts in the stool, there is probably added to the neuropsychogenic factor a true catarrhal inflammation of low grade, and this must be considered in the treatment;—a smooth diet, oil by rectum, perhaps small doses of castor oil, anti-spasmodics and mild sedatives.

It is well to remember that in mucous colitis the whole colon is not always involved, that the left side is more likely to be involved than the right, but that if the condition is rather sharply localized in the upper right, or the lower right, quadrant, it may almost exactly simulate appendical or gall bladder disease. It has even lead to operative treatment which is always unsuccessful and usually harmful.

One has no time here to even touch upon the problems connected with amoebic dysentery, so much in the medical mind at the present time, but it is worth remembering that the chances of finding motile forms or cysts are increased more than threefold if the stool is obtained through the sigmoidoscope and examined immediately rather than by the usual procedure. Incidentally, as regards the treatment of chronic amoebiasis, we have found a combination of earbarzone or stovarsol by mouth, Yatren or vioform by rectum, and possibly emetin hypodermically, most effective. If properly administered, the last drug has not harmed the myocardium in our experience.

*Treatment:* And now at a prolonged last, a short excursion into that most unsatisfactory realm, treatment! Yet after all, it is successful treatment that the patient wants more than diagnosis, for he often believes, with Mahomet, that '*God has not inflicted disease upon us without at the same time giving us the remedy.*'

Treatment, unfortunately, is built upon shifting sands, it is swayed by the eult of the moment, it changes with the tide of public opinion, it is singularly liable to exploitation, it is often unscientific and unsound, it is sometimes dishonest. Our best help must come from the simpler things, from rest and exercise, from encouragement and suggestion, from re-education and simple physical measures. The same rule should apply to diet, but alas, this is not true, for in no field is there so little science, so much fad and foolishness. For example, it is not interesting that after millions of years with people living healthily and in the main happily on a mixed diet, it is suddenly discovered that foods that have hobnobbed happily together for aeons of time, suddenly became anathema to each other? Is it comedy or is it tragedy that Beaumont labored in vain and that Pavlov's epoch-making experiments are so soon forgotten; that the story of digestion torn from the jealous breast of Nature in

that conflict between the creative will of man and the hidden wisdom of the world, which seems to thwart it, should be cast aside? I often think, with Josh Billings, that it is better to know a little than to know a lot of things are not so.

Put not thy faith in newer fads in diet; diets with no meat, diets of lettuce and orange juice, diets where protein and carbohydrates never meet at table! I like to remember what my friend, Robert Hutchison, the English master of dietetics, once wrote: *'The man who retires from business having nothing else to do, makes his health his hobby and collects new diseases as another man collects stamps. The food faddist is perhaps the most malignant of this type. Vegetarianism is harmless enough though it is apt to fill a man with wind and self righteousness.'* After all, a wise man is the best judge of his proper diet and a man cannot be a perfect physician save of himself alone.

I often wonder what the God of Medicine, Aesculapius, would say to his father, the great Apollo, if he looked down from high Olympus upon us little mortals in the world below. Would it not be—*"Why, my Father, has man not profited more from all the knowledge that has come to him, born of the centuries of striving of the great, spelling their travail, their struggles, their many failures, their few successes, wrung from the very womb of this old Earth that guards her secrets so jealously."*

*"These, the great leaders, have taught men the principles of diet and the physiology of food, and yet every new dietetic fad is followed madly. They have told them that peace and serenity are necessary for perfect digestion and yet they drive ever more madly through this mechanical age. The normal intestinal flora has been shown to them, and yet to these harmless organisms have been ascribed the cause of many diseases, and from them vaccines prepared, supposed to be imbued with divine power. The normal function of the colon has been shown them and yet mighty rivers have been diverted from their courses to supply the needs of one great city alone, the new Bagdad on the Hudson; a treatment supposed to wash away impurities, to cure and prevent disease and bring back eternal Youth. Even the humble colon bacillus is plucked from its*

*home where it has slumbered peacefully for generations and transplanted, that sickness may be abated and death postponed."*

*"How can this be, my Father?"*

And I can hear Apollo reply—*"Be not worried, my son, for while there is much that is false and much that is absurd in all this, there is perhaps also a grain of truth. The food faddist is not always mad! Change of intestinal flora may sometimes help; irrigation is not always harmful; and even a vaccine of intestinal origin may sometimes do some good. Did it not take millions of years for man to emerge from darkness to the first faint glimmerings of dawn? Did the next six thousand years bring more than a few stones for the foundation of knowledge and have not some of these already crumbled away? While in the last century, knowledge has come so fast that Man, blind, groping Man, cannot digest it."*

*"For a hundred years is but a drop of water in the ocean of life, a grain of sand in the desert of Time. Knowledge has come in great abundance, but Wisdom lags far behind."\**

And now our voyage is over and we are safe at anchor. We have visited many parts and sailed many seas. Some clearly marked and easy to navigate; others still so shrouded in fog that we must travel them slowly and with the utmost care—a voyage which, if it has taught us nothing else, should have told us that to traverse safely its main channel, its tributaries and its backwaters near and far, we must not only know well our main route, but know something of all the other paths that altogether make up this cosmos which we call man. After all, the body is not the mere summation of its constituent parts—physical, psychical, spiritual; each has some tangible or intangible connection with every other. In no system is this more true than in the digestive tract, for it is a glass in which may be mirrored any disease or dysfunction elsewhere. In no system is that wisest of all medical rules more absolutely true—first study the whole, then the part.

\* (T. R. B. The Story of Digestion and Indigestion, International Clinics, Vol. IV, Series 42).

## Migraine: A Common-Sense Approach

By

LIBBY PULSIFER, M.D.\*  
ROCHESTER, NEW YORK

### 1. GENERAL STATEMENTS

IT is not common for a single patient to have all his attacks go through the complete syndrome of prodromata, headache, nausea, and vomiting. Such occurs occasionally. Instead, usually the patient suffers from a fraction of the syndrome, perhaps two of the above features, the pattern of each attack being very similar to the pattern of other attacks except in severity.

As evidence of the considerable degree of disturb-

ance in the nervous systems of some patients during attacks of migraine, I have prepared charts illustrating the change one patient had in his fields of vision. (Chart No. I).

Additional support of the idea that the restless, hypersensitive, migrainous type of person is found mostly in the upper strata of society lies in the fact that during several years experience in the charity clinics of two hospitals, I have encountered not more than two dozen patients in whom migraine was recognized, while in eight years of private practice, I have

\*Associate Physician, Rochester General Hospital; Instructor of Medicine, School of Medicine, University of Rochester. Submitted May 17, 1935.



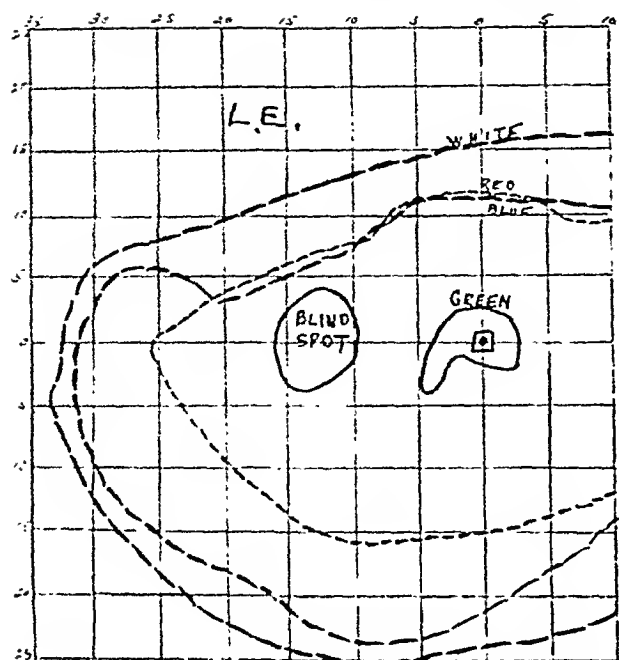


Chart 1-A. Fields of vision when suffering from moderately severe migraine. Patient L. J. 1° test object.

made this diagnosis more than three hundred times, or in 13% of all patients seen.

The tendency to have migraine is an inheritable characteristic which seems to behave like a dominant in Mendel's Law (1). However, I believe that the in-breeding of migrainous individuals with each other, or with allergic, depressive dipsomaniac, epileptic or otherwise mentally unstable individuals, usually may result in the production of offspring more migrainous, allergic, depressive, etc., than is the case when migrainous persons have children by those whose ancestry is quite free from these disorders. (Chart No. II).

## 2. GENERAL MEASURES EFFECTIVE IN TREATMENT

Granting that migraine is "the most baffling and dramatic form of all headaches, a snag over which the medical profession has stumbled for centuries," and granting the hopelessness of avoiding the tendency to suffer with the exasperating and disabling malady by choosing parents who are entirely free from this disorder, it does not follow that there is nothing to be done for the unfortunates who are afflicted. In dealing with these sufferers, the single therapeutic endeavor which, I believe, will bear the most fruit is a determ-

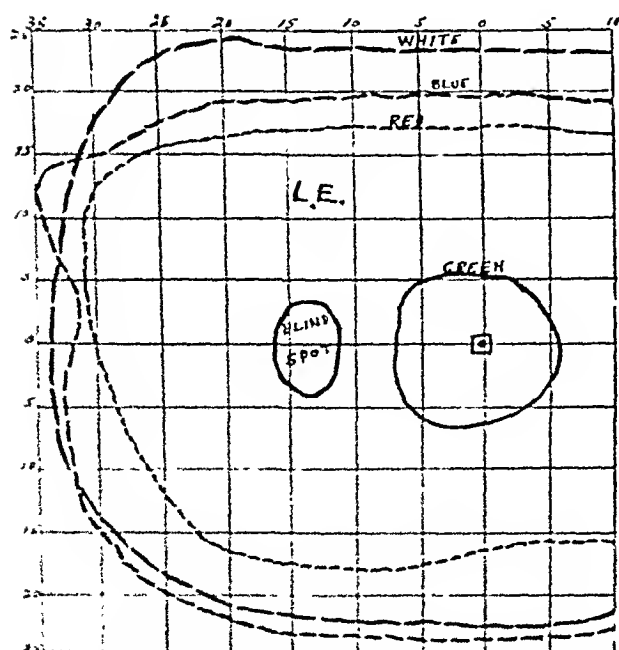
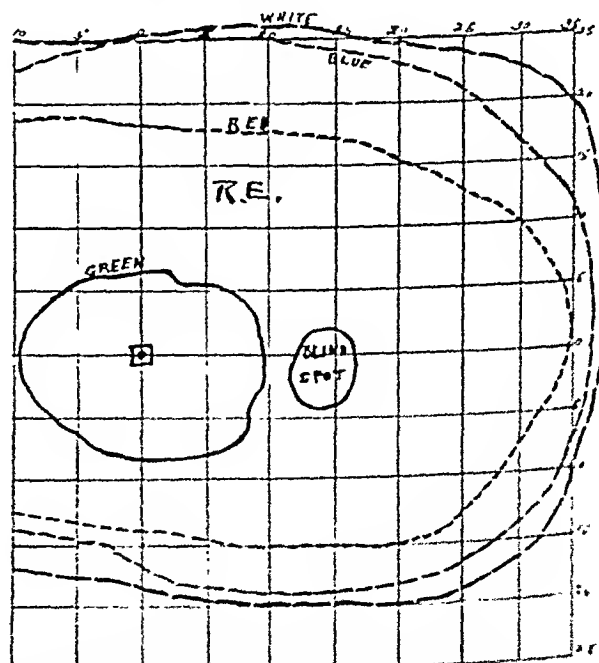


Chart 1-B. Fields of vision when no migraine. Patient L. J. 1/4° test object for white, 1° for other colors.





ined effort to maintain in the patient, nervous and emotional equilibrium and tranquility. Many of these people, when first seen, are nervous and emotionally disturbed with a consequent high degree of affectivity. There is very little doubt that this state of being in "high gear" renders them much more likely to have attacks of hemicrania, just as others in such a state are more likely to have peptic ulcers, angina, asthmatic attacks, bowel spasms, and the like.

As soon as the diagnosis is certain, it usually is highly worthwhile patiently and considerately to tell the patient in some detail the nature of his affliction, since, as Alvarez has quoted, the successful "conquest of fate is not by struggling against it, nor by trying to escape from it, but by acquiescence." (2) The peace of mind that accompanies this understanding may in itself seem to lessen the frequency of attacks. He may

sponsibility for the machinery which delivers illuminating gas to his city. He has had attacks of hemicrania since age sixteen, in recent years at least once a week. Pain starts usually in the morning in one eye, and, increasing in severity, extends over the side of his head. This is soon followed by nausea and vomiting (sometimes vomits as much as fifteen times). The whole attack lasts one day. Next day, he feels quite well again. Sister has similar attacks, as also had mother.

No other findings of note save tender transverse bowel and fermentative stools.

The situation was thoroughly talked over. The diet was slightly modified and coffee was omitted. A program of relaxation at meal times and recreation was advised. He started to take phenobarbital 1 grain each night.

On November 8, 1934, he reported that he had had only three very slight headaches in the six weeks since first seen. Each of these was relievably by a simple analgesic.

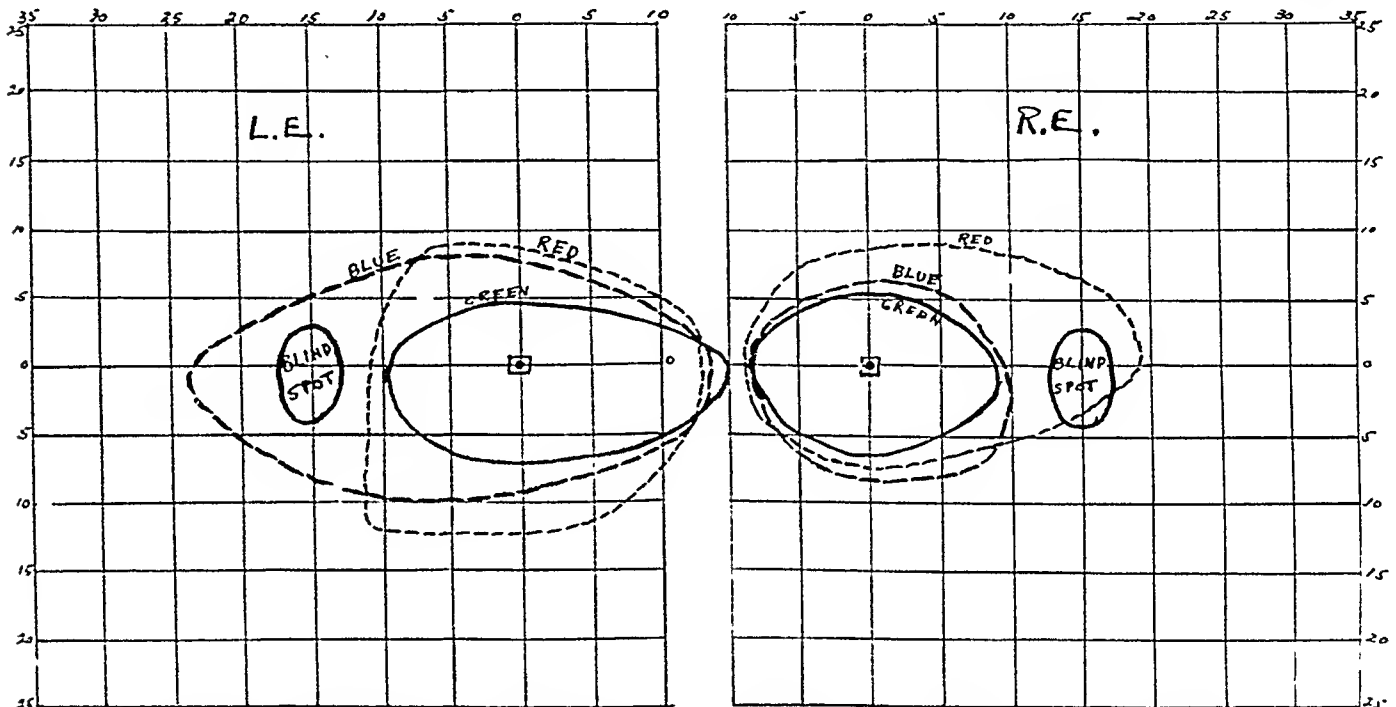


Chart 1-C. Fields of vision when suffering from severe migraine. Patient L. J.  $\frac{1}{2}^\circ$  test object.

so be persuaded to stop seeking "cures" in physics, doses, faddish diets, and operations (any of which may be contributing to his disability) and instead accept a common sense approach to his trouble.

Besides psychotherapy, a period of daily sedation may be indicated. I find most valuable for this purpose the administration of small doses of phenobarbital or bromide, never to the point that the patient may be conscious of sleepiness or depression.

An example of the result of treating a proper patient by these principles alone is seen in the following case history. (Only those cases are included in my series in which every reasonable means has been employed to make an accurate diagnosis. A complete history and physical examination with blood counts, blood Wassermann and urinalysis have been done on every patient studied. X-ray examinations, other laboratory tests, and consultations with various specialists have been freely resorted to whenever indicated).

*Case 1.* A thirty-one year old engineer, seen September 26, 1934, works long hours and takes very seriously his re-

There had been no nausea or vomiting or necessity for staying home from work. Patient was very pleased.

His condition remains equally good to date (six months).

The "ultimate prognosis in such a case must depend upon the physician's success in "selling" an intelligent enough patient an understanding of himself and his malady so that an altered attitude and behavior toward his environment and toward his affliction may be assumed. Relapses may be expected occasionally when the rate of nervous activity again may be raised in response to insufficient rest, coffee, or environment difficulties beyond the patient's control, but improvement usually may be expected by psychotherapy and resumption of management. Others who are more unstable and less intelligent, or whose environmental difficulties are insurmountable are, accordingly, increasingly difficult to relieve.

*Second Point in Therapy: Precipitating Factors:* A diligent search for them will, in many instances, reveal definite factors which precipitate individual attacks in individual patients. I am convinced that these factors induce attacks in susceptible individuals be-

cause they disturb the nervous and emotional balance in sensitive patients.

*Example:* There was the case of the conscientious, thirty-five year old assistant to a fussy dentist, who also kept house for an euphoric, worthless husband. She suffered, as did her mother, frequent, severe, often prostrating attacks of unilateral headache which she was able to avoid only when she escaped from job and husband for several weeks.

A man who ran a storage-battery sales and service station was compelled to stay away from work about one day a week because of attacks of severe pain starting deep in the right eye, which extended over half his head, and cul-

A housewife, who tended to gain weight, had scanty eyebrows, a dry skin, and a basal metabolism of -22%, has obtained relative freedom from attacks for a year while taking a daily ration of thyroid extract.

Attacks commonly occur in women at menstrual time. These may often be eliminated or controlled by appropriate measures. I have tried various endocrine substances in such cases with no encouraging results.

Chocolate may seem frequently to induce attacks. One young mother whose prostrating sick headaches came four or five times a month had only one attack in two years when she omitted eggs from her diet. In my series there was discovered allergy or a family history of allergy in

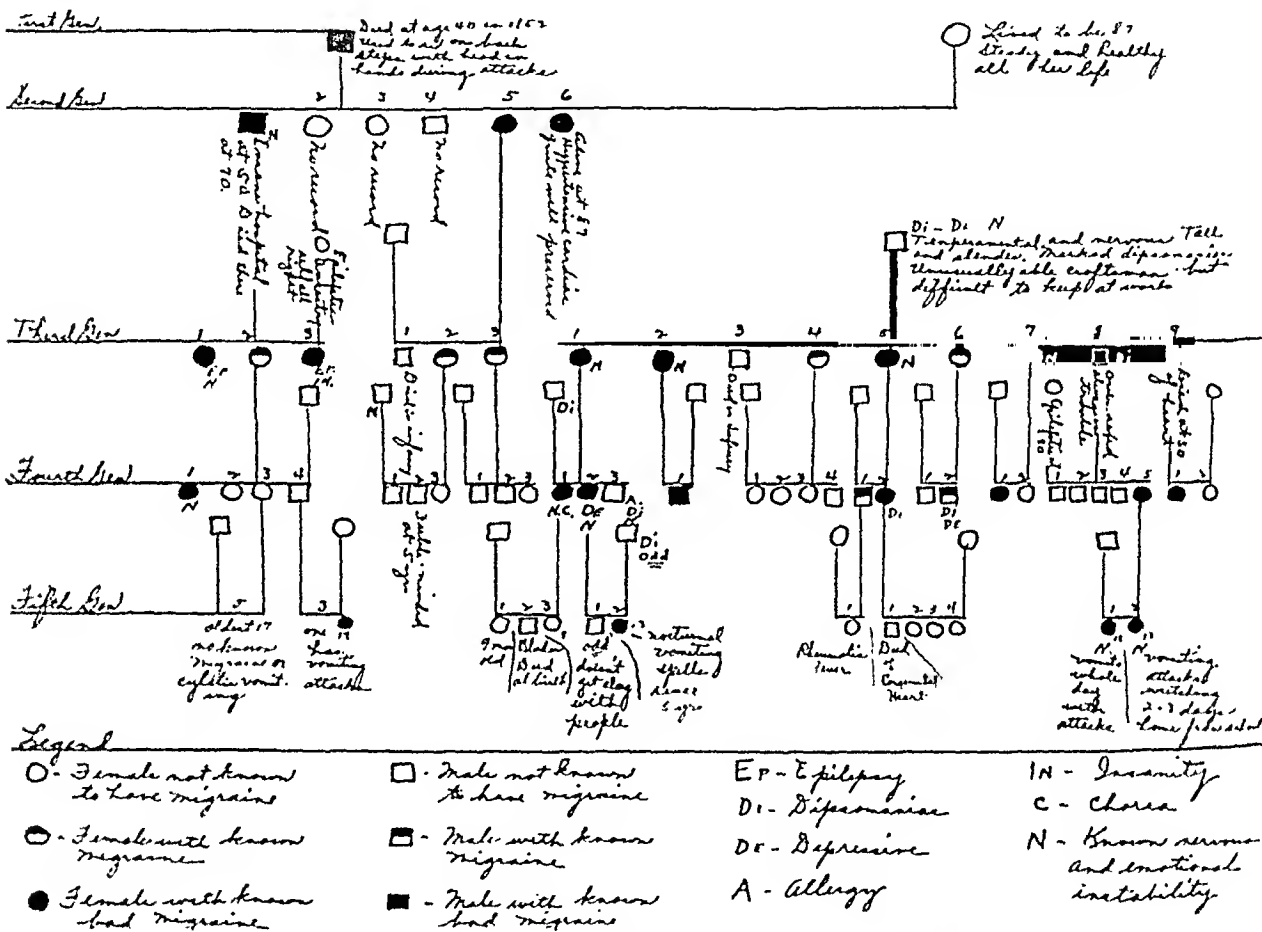


Chart 2. An authentic migraine family inbred with dipsomania.

minated in repeated retching and vomiting. These attacks occurred over a period of ten years, during which time he had taken almost daily cathartics with consequent abdominal distention and pain. In 1927 gall bladder (no stones) and appendix were removed; 1928, all teeth removed; 1929, \$100 was paid to a doctor and \$100 to a chiropractor; 1930, a tonsillectomy was done. All these things were undertaken in the hope of curing his "bilious attacks." He was seen in 1931 and put on bowel and migraine management with complete relief of all his symptoms. Two or three times a year he needs aspirin and amidopyrene; he secures relief from these remedies.

A lawyer was relieved of migraine by teaching him to avoid dyschezia.

Relief came to a doctor's wife when her peptic ulcer was successfully managed.

An ice man had no more attacks when a gross refractive error was corrected.

only 5%. This is not in line with the reports of Balyeat, Rowe, and others, but these men, known as "allergists," must see patients who are predominantly allergic. Many of that class of people probably also have inherited true migraine and their attacks may be induced by the upsetting effect of ingesting proteins to which they are allergic.

A telephone line man who smoked thirty cigarettes a day obtained relief from his migraine, his hypotension (100.60 to 116.70) and his lowered basal metabolism (-23 to -1%) when he stopped smoking.

*Measures to Relieve Attacks.* At the onset, attacks may often be relieved by one of several simple analgesics (3). Some patients should have such a remedy always on their persons. Strangely enough, difficulty is sometimes encountered in persuading the sufferer promptly to take his remedy, although he may have it

in his pocket and know it will bring relief. Here, then, the "salesmanship" of the physician is again put to test. After attacks are in full bloom, many patients can obtain no relief at all except with "knock-out drops." In the last five months, we have used "cibal-gine" (4) intravenously thirty times in twenty-six cases suffering with all stages of the migraine syndrome with results so good as to be astounding. With a few exceptions, the headache disappeared immediately, and the patient felt relaxed and comfortable. Ergotamine tartrate (marketed as "gynergen") may increase menstrual discomfort, and cause vomiting. Three patients of mine have reported it as ineffective. However, the encouraging reports of others warrant continued trial of this preparation.

Although daily rations of calcium are said to help some patients, I have not seen any that I felt were benefited by its use.

For "the migraine state," sodium thiosulphate (5) or sodium bicarbonate (6) *i.v.* at intervals of five to seven days, sometimes may seem to help, or perhaps this relief is due to the repeated contact with the physician.

*Treatment Fails in Three Types:* There are in my experience just about three classes of migraine sufferers of whom the treatment is usually discouraging.

One of these is illustrated by the case of a housewife seen four years ago. All of her relatives seemed to have migraine. She was perfectly well otherwise, and her attacks, lasting two or three days, were always prostrating. I studied her for eight months without ever finding precipitating factors, or giving her any relief whatever, even though she cooperated splendidly. Such cases are really uncommon.

Secondly, eighteen percent of my series of migraine patients were definite "insanity equivalents." (7) Such are so unstable and so poorly equipped mentally that they are beyond much help.

Fortunately only a few patients fall into this third class which is very difficult to treat. It is exemplified by a fifty year old lumber dealer, who, in spite of the fact that his sister, brother, and mother had similar attacks all their lives, insisted that he must have a physical cause in his abdomen for his ailment. He was garrulous and hard to manage. He never cooperated and no relief was obtained. Subsequently, against my advice, he had a normal gall bladder removal. He died post-operatively. Unfortunately a surprising number of these patients who suffer with migraine come to believe that their disorder is referable to the liver or gall bladder, or sinus, nose, tonsils, teeth or even appendix. Considerable numbers of them have had surgery without adequate indications and without any relief.

## RESULTS OF TREATMENT

The results of our treatment in 150 consecutive cases, chosen only because they had been followed suffi-

ciently long (none less than six months—most more than three years) that a fair judgment could be made, showed that 2.5% seemed to be worse, 22% were not improved, and 73% showed a very gratifying improvement. Usually the interval between attacks has been very much lengthened, and the attacks themselves are much less severe. 2.5% had no more attacks. This improvement in 73% of all cases seemed certainly to warrant the painstaking effort of the physician, and the effort and expense to the patient.

## SUMMARY

Charts illustrating the changes in the fields of vision of a patient suffering from migraine are shown.

A chart is presented showing the incidence of migraine in an authentic five generation study of a family; which also illustrates the presumed effect on the offspring of inbreeding a dipsomaniac with a person who suffers with severe migraine.

In 13% of my private patients migraine was a major problem.

General measures effective in treatment are outlined and illustrated by a number of case histories.

As factors which may precipitate trouble with migraine, the following were pointed out: Environment, cathartics, dyschezia, peptic ulcer, refractive errors, hypothyroidism, menstruation, food allergy, excessive smoking; there must be many others.

Means for the relief of individual attacks, especially by "cibal-gine" gr. *i.v.* were suggested.

Treatment failed in the case with unusually strong migraine heredity, the insanity equivalent, and the uncooperative.

73% of our cases showed a gratifying degree of improvement.

## CONCLUSIONS

Migraine is an inherited malady and inbreeding of migrainous individuals with unstable individuals increases the likelihood of the occurrence of migraine in the offspring.

Migraine is common.

Migraine attacks are precipitated by disturbing, in a variety of ways, the nervous and emotional tranquility in susceptible persons.

In treating migraine, one must be content with lessening the frequency and severity of attacks and the discovery of a remedy which will bring relief when attacks occur.

Simply to hand a migraine sufferer a diet or a prescription and send him on his way is bad medicine. A migraine case is a challenge to the thought, understanding and "salesmanship" of the physician. Hard work on such a problem, may, in more than seventy percent of cases, yield gratifying results.

## REFERENCES

1. Buchanan, J. A.: The Mendelianism of Migraine. *Med. Rec.*, 98, pp. 807-808, 1920.
2. Alvarez, Walter C.: Nervous Indigestion, First Edition, Paul B. Hoeber, Inc., New York, p. 168.
3. We never use opiates or cannabis. For analgesics used for relief of attacks: Beckman, Harry: Treatment in General Practice, second edition, Vol. II, W. B. Saunders Co., Philadelphia and London, 1934, p. 635.
4. Cibalgine-Ciba Company, New York; Society of Chemical Industry in Basle-Switzerland.
5. "Sulfaetol" brand of sodium thiosulphate, Metz. Personal communication from Robert E. Johnnesen, M.D., S. Michigan Blvd., Chicago, Ill.
6. Personal communication from Paul Garvey, M.D., Rochester, N. Y.
7. Alvarez, Walter C.: Insanity Equivalents and the Gastro-Enterologist. *Am. Jour. Dig. Dis. and Nutrit.*, Vol. 1, July, 1934, p. 305.

# The Validity of Fractional Gastric Analysis\*

By

FRANCES A. HELLEBRANDT, M.D.

and

ELIZABETH BROGDON, M.S.

MADISON, WISCONSIN

**T**HE function of the digestive processes is to change the foodstuffs introduced into the gastro-intestinal tract physically and chemically, so that they may be assimilated and made available to the tissues of the organism as a whole. Changes in the consistency and composition of the foodstuffs administered should be a gauge of the adequacy of these processes under varying physiological conditions. This approach has been largely ignored. The attack has been one of differentiating from the gastric contents the components poured out by the various types of secreting cells present in the mucosa, and of measuring functional competence in terms of enzyme strength or acid concentration. Clinical observations have been limited almost wholly to the latter procedure. A stimulus to the secreting cells of the stomach is administered and their response is measured during its effective period. Such a procedure is valid only if the intensity of the stimulus is controllable, and if the part under study may be freed from augmenting and inhibiting influences other than those attributable to the specific substance administered.

Both of these criteria of validity have been abundantly attacked since the introduction of fractional gastric analysis. The first has been adequately met as is evidenced by the evolution of the test meal. The stimulant has been gradually made more constant. That to at least one type of gastric secreting cell, may now be introduced parenterally in a quantitatively measurable dosage.

More serious difficulties arise in meeting the second criterion. The complexity of the processes involved may be illustrated by summarizing the factors which must affect the acidity of the gastric contents, which is the aspect of gastric activity most used as a measure of functional sufficiency in man. First, if a meal is used as the stimulant, it has a diluting and neutralizing effect which adds itself to that already produced by saliva, regurgitated duodenal contents, and the secretions of the chief and mucus cells. The fluid under study is evacuated from an organ which cannot be isolated from contiguous parts of the alimentary tract, and which contains more than one type of secreting cell. Second, the secreting cells are susceptible to stimulating in a variety of different ways, reflex, humoral, mechanical, vascular, motor and chemical. We do not yet possess practical selective stimulants capable of calling into activity isolated secretory mechanisms. Third, the secreting cells are in addition affected by extragastric reflex and humoral influences which may be either inhibitory or stimulatory. One may con-

clude, a priori, that with methods applicable to man, the repeated administration of a *constant* stimulus cannot call forth a quantitatively reproducible response. If the results of gastric analysis are significantly variable, they cannot be used for diagnostic purposes. However, the contour of the acidity curve has been taken as the basis for the classification of the behavior of the stomach (Bennett and Ryle, 1921), and various types of curve are looked upon as pathognomonic of specific diseased conditions (Lyon, Bartle and Ellison, 1921; Rehfuess, 1927).

Bloomfield (1932) has vigorously defended the physiological soundness of the results of human studies. He believes that accurate measurements of gastric secretion can be made in man. In his hands (Bloomfield and Pollard, 1933) repeated tests of the same person have yielded almost identical results. These are reported to be so constant, "that they can almost be used, like finger-prints, as marks of identification." Evidence in support of this is not presented. The technique of Bloomfield and Pollard differs from that usually employed in two major respects. Histamine is used as the secretory stimulant, and the gastric contents are continuously aspirated during the test period (1929). Even before the development of these refinements in technique, Bennett and Ryle (1921) reported identical curves after the repeated administration of oatmeal gruel. This, however, has not been the usual experience, and the reliability of fractional gastric analysis as an acceptable method of study has been repeatedly questioned (Crohn and Reiss, 1917; Lyon, Bartle and Ellison, 1921; Kopeloff, 1922; Baird, Campbell and Hern, 1924; Van Zant and Alvarez, 1931).

There is little objective evidence in the published literature demonstrating ranges of normal gastric secretory variability. The most extensive observations are those of Bell and MacAdam (1924) who studied one man on 20 consecutive days and who present a statistical analysis of their data. Although the standard deviations and coefficients of variation are large, these findings have been repeatedly cited in support of the reliability of fractional analysis as a diagnostic procedure. The observations were made after the ingestion of gruel. No similar series have been reported for other meals. The object of our study was, therefore, to make an investigation of the comparative reliability of three different types of secretory tests in common use.

## METHODS

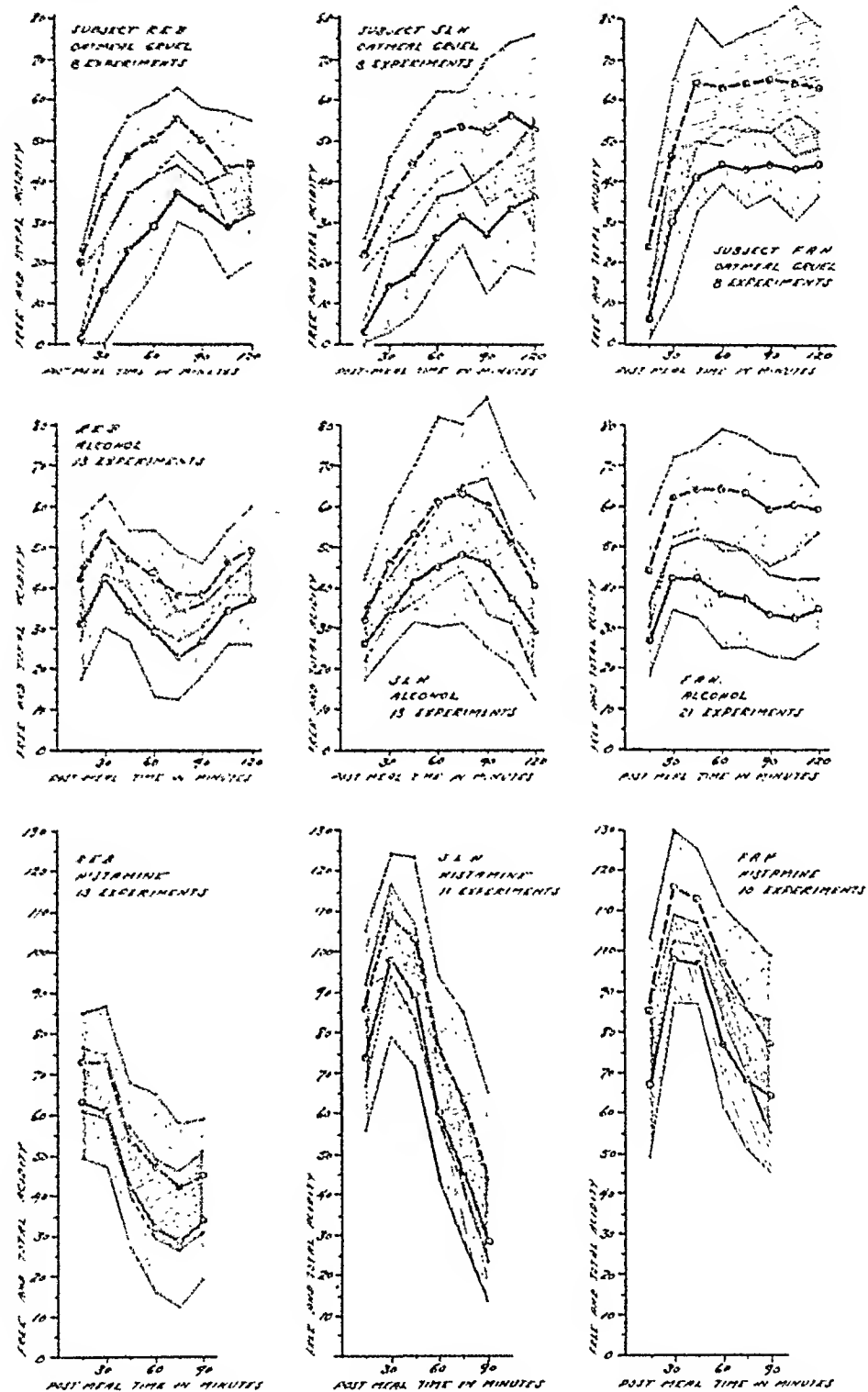
Observations were made on normal, healthy young adult women, accustomed to gastric intubation and without history of gastro-intestinal disease. A standard duodenal tube (Rehfuess) was swallowed without lubrication or the ingestion of fluid until the metal tip reached the most de-

\*From the School of Medicine, University of Wisconsin, Department of Physiology. Supported in part by funds from the Wisconsin Alumni Research Foundation.  
Received April 27, 1935

FIGURE 1

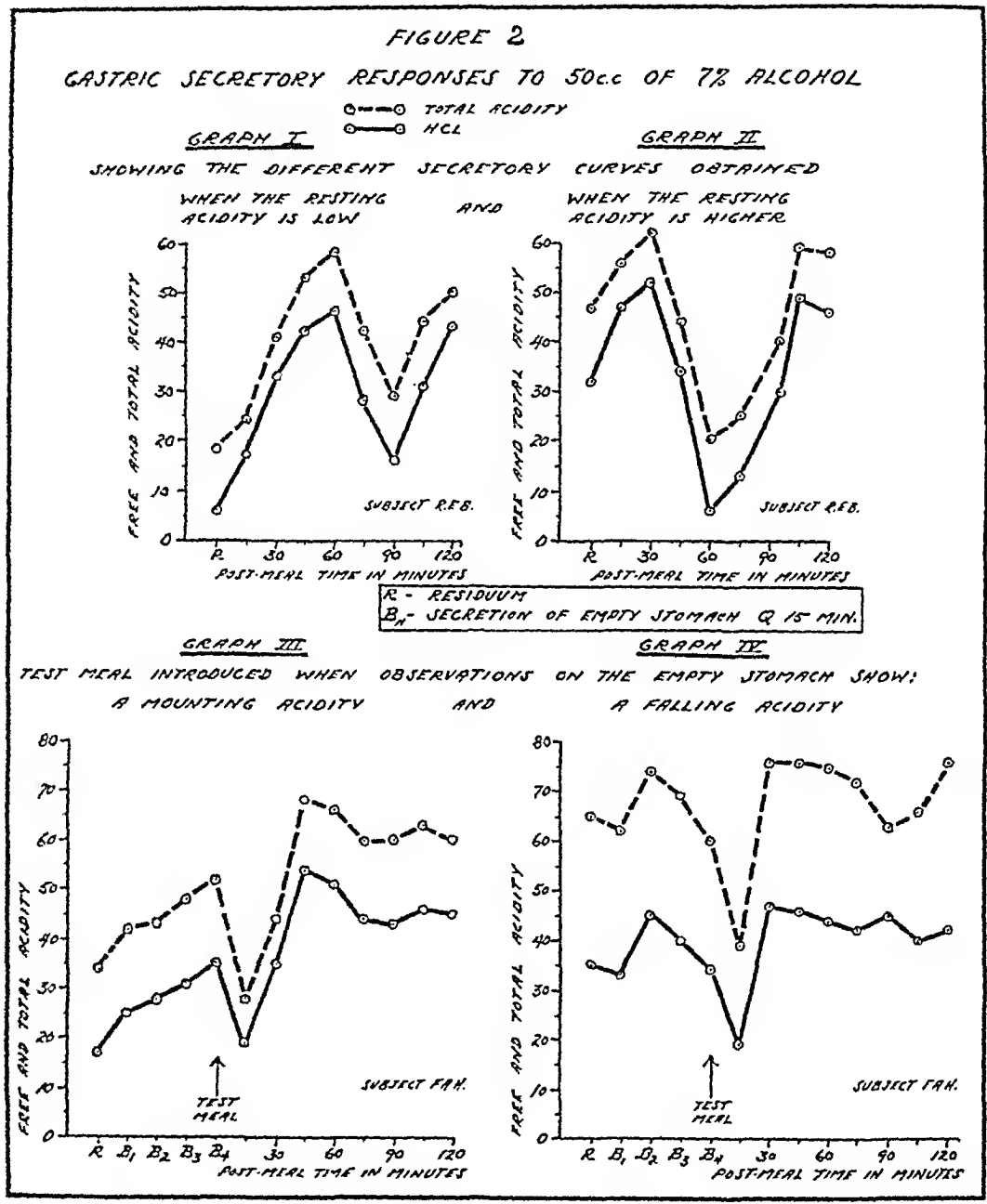
GRAPHS SHOWING THE DISPERSION ABOUT THE AVERAGE GASTRIC SECRETORY RESPONSE OF THREE SUBJECTS TO THREE DIFFERENT TYPES OF TEST MEALS

—○— TOTAL ACIDITY-ARITHMETIC MEAN      —○— FREE HCL-ARITHMETIC MEAN  
 - - - - - 6 OF THE DISTRIBUTION-TOTAL ACIDITY      - - - - - 6 OF THE DISTRIBUTION-FREE HCL



pendent pole of the stomach. Observations were commenced 14 to 20 hours after the last meal. The fasting contents were completely aspirated before the administration of the stimulant. Secretion was induced by 400 c.c. of strained, warm oatmeal gruel, taken by mouth with the tube in situ; by 50 c.c. of 7 per cent alcohol introduced through the tube; and by histamine in a dosage of .1

When secretion was stimulated with histamine by the par-enteral route, the full gastric contents were withdrawn at quarter hour intervals. Free and total acidity were determined by titration with N/10 NaOH, using dimethylaminoazobenzene and phenolphthalein as indicators. Results are expressed in terms of the number of cubic centimeters of decinormal sodium hydroxide necessary for the



mg. 10 kg. A 1:1000 solution of ergamine acid phosphate was used by hypodermic injection. Saliva was either continuously expectorated or removed by suction. The subjects refrained from mental and physical activity during the periods of observation, which varied from 90 to 120 minutes. When meals were used as the secretory stimulant, samples of the gastric contents were aspirated every 15 minutes. Since the gastric contents are not a homogeneous mixture, samples were aspirated and re-introduced several times before removal for purposes of analysis.

neutralization of one hundred cubic centimeters of gastric juice. To measure the degree of dispersion, the standard deviation of the distribution was calculated in the usual way.

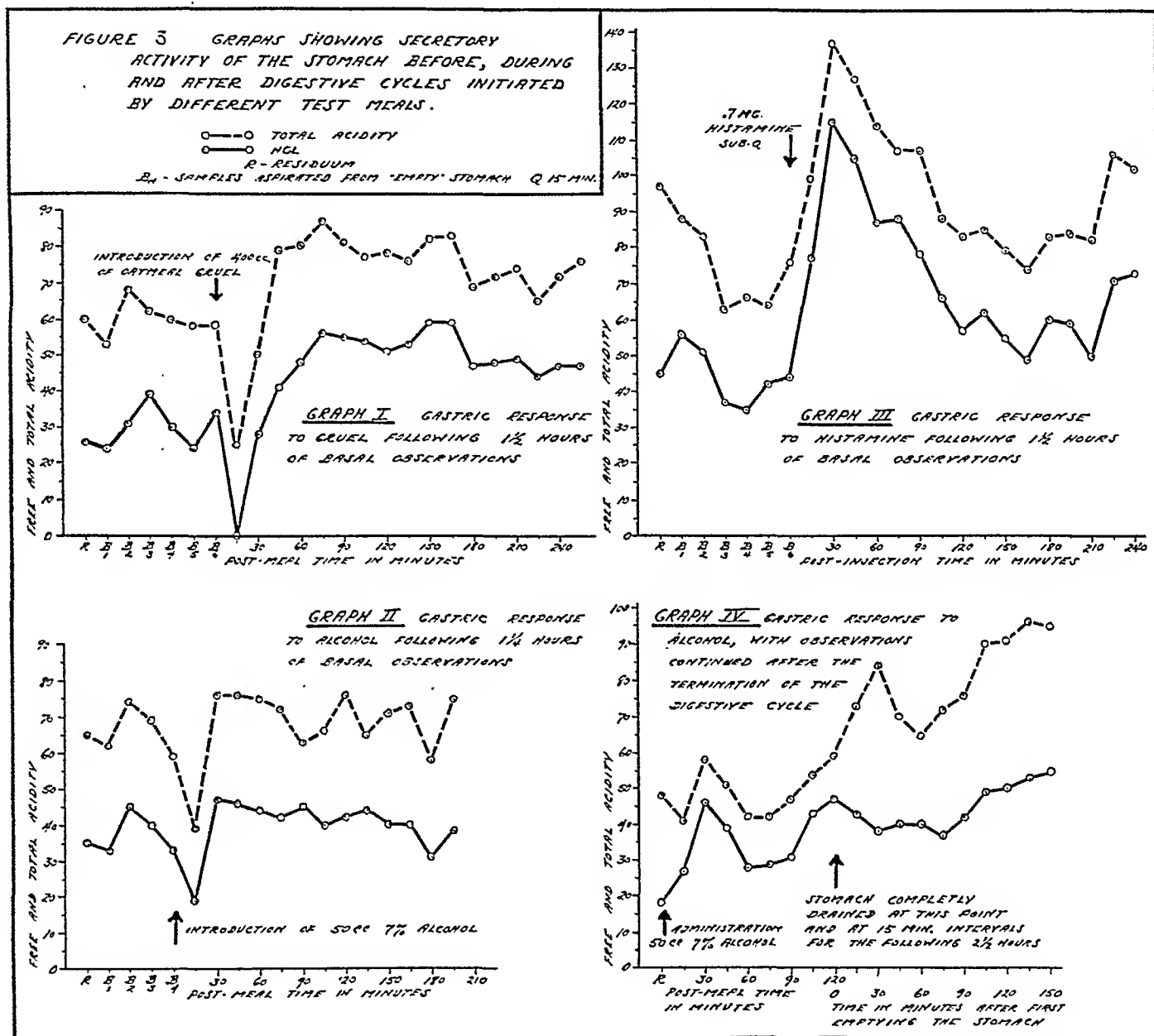
RESULTS

A total of 105 experiments were performed on 3 different subjects during a period of 8 months, 24 after the administration of gruel, 47 after alcohol and 34 after histamine, as illustrated in Figure 1. Both the



average secretory response and the standard deviation of the distribution have been graphed for each subject and for each stimulant. Examining the figure vertically, the response of one subject to the three different secretory stimulants may be compared; examining the figure horizontally, the response of three normal subjects to a single meal may be compared. It is evident at a glance that variations are great when healthy human subjects are examined repeatedly under identical conditions and by a rigorously controlled experi-

nating series of active and quiescent cycles, instigated by the intermittent ingestion of stimulating foodstuffs. Our findings are not in accord with this hypothesis of gastric secretory function. First, the curves which result from the plotting of acidity values do not invariably rise and then fall. The predominant trend may be quite the reverse. If Graphs I and II of Figure 2 were superimposed, the height of secretory activity in the former would roughly correspond in time to the period of lowest acidity in the latter. Further, the



mental technique. The scatter of the gruel series is comparable with that demonstrated by Bell and MacAdam. The small alcohol meal is almost as strong a secretory stimulant as is gruel, and the acidity response to it approximates that of gruel in its variability.

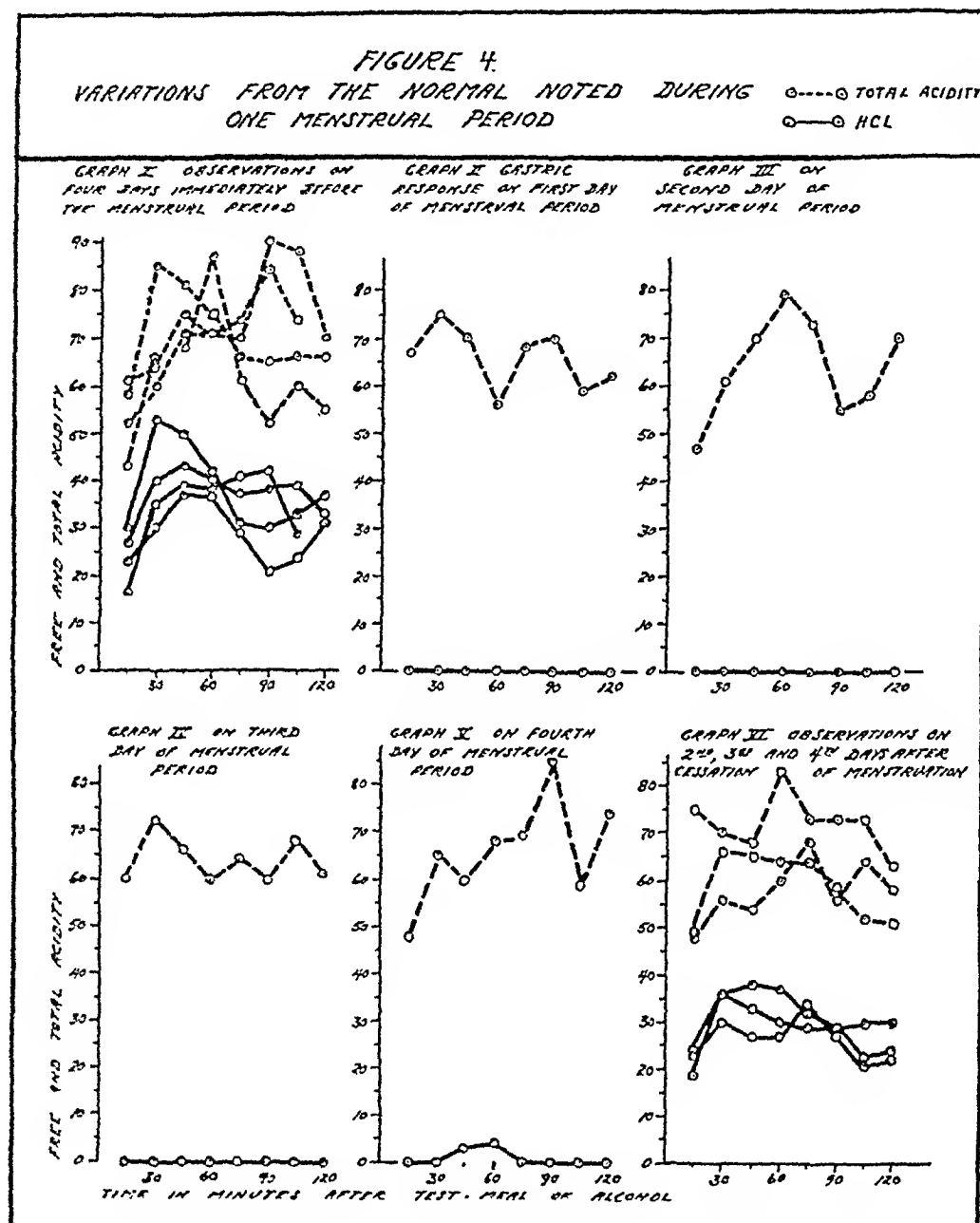
Rehfuß (1927) divides the secretory aspects of digestion into three phases, the periods of adjustment, the acme and the readjustment. They correspond to the intervals of increasing, peak and falling secretory velocity. He conceives gastric function as an alter-

curves show that the initial functional state following the aspiration of the fasting residuum during the interdigestive phase of Rehfuß is not constant, and that they strongly suggest that the post-prandial response may be related to the pre-stimulatory condition of the stomach. This, however, is not substantiated by the curves presented in Graphs III and IV of the same figure but may be deserving of further study. Second, Rehfuß describes the ideal, normal, terminal period as one of declining activity, approaching that of the so-called interdigestive period of relative secretory quies-

cence. Many of our curves show no tendency to fall, as illustrated in Figure 1, and in Graphs I and II of Figure 3 where the post-prandial observations are continued for longer intervals. Not infrequently a delayed rise follows the post-prandial decline. Such spontaneous augmentations are demonstrated in Graphs III and IV of Figure 3. They may markedly exceed

of dispersion. Variability is very nearly equally great during all phases of the secretory cycle.

Histamine is the most powerful stimulant known to the ocyntic cells of the stomach and the peak acidity attained under its parenteral influence is appreciably higher than that following the ingestion of a test meal. The closer parallelism of free and total acidity and the



the heights to which acidity is stimulated by the administration of a test meal. According to Rehfuess, the digestion of vegetables is characterized by a rapidly declining acidity, that of meat by a slow decline. It seems unjustifiable to us, to give so specific an interpretation to the contours of such inconstant curves. Third, Rehfuess reports the period of adjustment as the most unstable. This is not borne out by our graphs

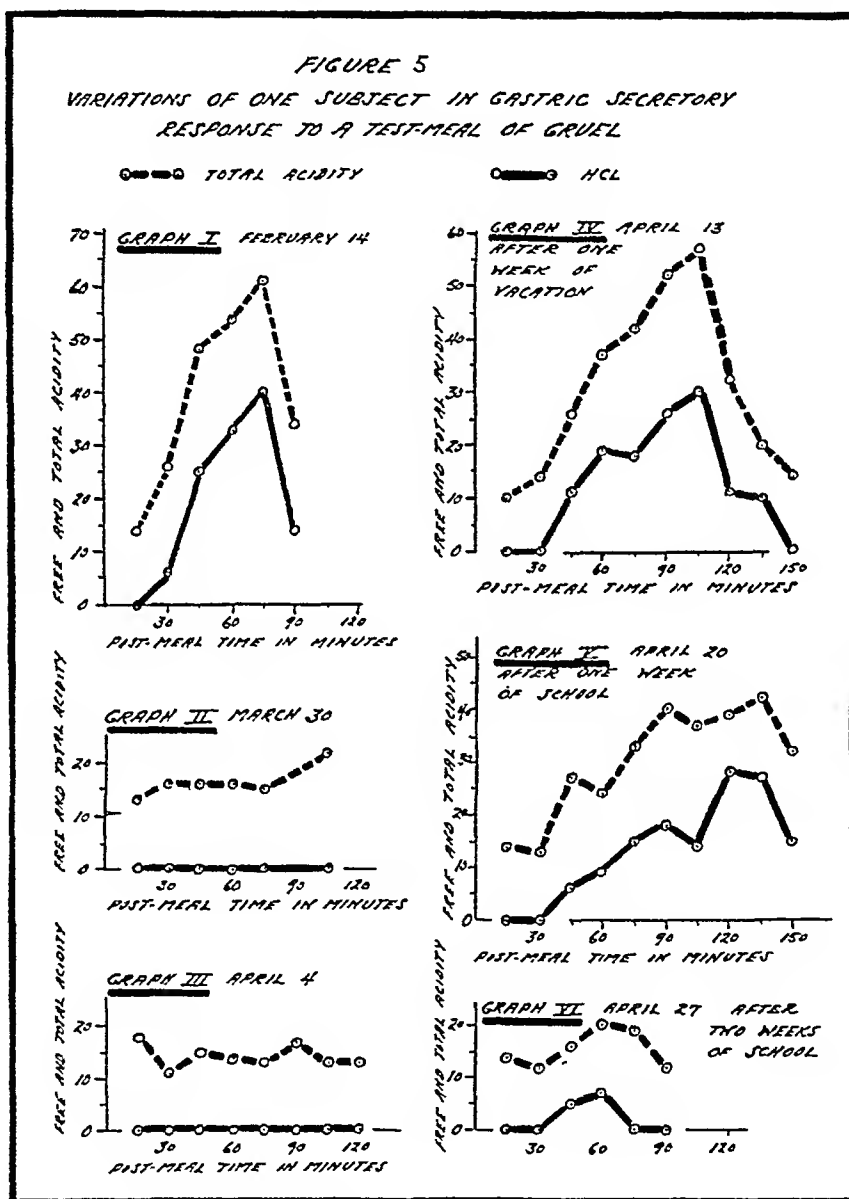
consequent overlapping of the areas mapping out dispersion, give a false impression of improved stability. In reality, histamine curves are scarcely more reproducible than those following the administration of stimulants less susceptible to exact quantitative duplication. The results of R.E.B. are atypical in that peak acidity was reached within the first 15 minutes and never approached the high levels consistently attained

by both S.L.H. and F.A.H. Unlike the experience of Bloomfield and Polland (1929), the hypodermic injection of a fresh 1:1000 solution of ergamine acid phosphate in the recommended dosage of .1 mg./10 kg. invariably was associated with unpleasant symptoms, brilliant flushing, a sensation of heat, and throbbing headache. These were especially evident in R.E.B. and it was deemed inadvisable to increase her dosage.

Secretory variability also may be a reflection of changes in general bodily condition. Two groups of

natural foodstuffs. Histamine adequately may measure the limits of the latent secretory capacity of the parietal cells, but it is of equal interest to know what percentage of their full functional power these same cells exhibit under changes in the physiological condition of the organism *in toto*.

The daily, single aspiration studies of Van Zant and Alvarez (1931) demonstrated a tendency for gastric acidity to be cyclic, low during menstruation and higher between periods. Figure 4 shows the sudden



data demonstrate the development of transient an-acidity and illustrate the extreme sensitivity of gastro-intestinal mechanisms to insensible gradations in fitness. Bloomfield and Polland (1933) classify this type of an-acidity as "false" and predict that such oscillations in function will cease to appear when test-meal methods are discarded in favor of the histamine technique. In this respect histamine may be looked upon as masking a condition of considerable interest. Even though the parietal cells possess the ability to secrete free HCl when stimulated by as powerful an agent as histamine, they do not always do so when under the influence of less stimulating chemical substances or

appearance of achlorhydria in a normal healthy young woman with the onset of a menstrual period which was unaccompanied by any signs or symptoms of disturbed function. Free HCl promptly reappeared with the cessation of menstruation.

The subject whose graphs are illustrated in Figure 5 was a healthy young professional student in physical education. She had been under observation continuously for about 4 months prior to the date on which Graph I was obtained. Her gastric secretory response to oatmeal gruel had been in all respects normal. With the beginning of the second semester of the school year gradually she developed an hypoa-cidity until total

lethargy finally supervened. Her response to oatmeal gruel immediately before the spring recess is presented in Graph III. The succeeding graphs demonstrate the return of acid secreting ability after a week's vacation and the progressive re-development of hypacidity with the resumption of school work. The subject was conscious of no change in condition and there were no objective evidences of variation in fitness. Observations made during the long summer vacation showed widely oscillating degrees of acidity. Free hydrochloric acid was totally absent on 4 different occasions without detectable cause.

### SUMMARY AND CONCLUSIONS

Gastric fractional analyses were repeated from 8 to 21 times on 3 normal subjects after stimulation by oatmeal gruel, 7 per cent alcohol and by histamine. The average acidity values and the standard deviation of the distributions were plotted to show the reliability of the procedure.

From the results of 105 experiments, we conclude

that the secretory response of the stomach is highly variable in the normal subject, irrespective of the quantitative reproducibility of the stimulant used. Because secretion is affected via motor, mechanical, chemical, vascular, humoral and reflex paths beyond satisfactory control and by changes in general condition or fitness, the estimation of functional capacity in terms of the acidity response to a test-meal or to histamine as administered in these experiments is not a valid procedure.

These theoretical considerations substantiate the probable accuracy of the experimental observations. The contour of an individual acidity curve has little meaning, and deviations from it produced by conditions under study must be extreme before they can be considered statistically significant. Although fractional gastric analysis is of questionable value for quantitative studies of gastric function, it remains the method of choice for qualitative determinations of gastric acidity and for approximations of secretory capacity.

### REFERENCES

- Boyd, M. McC., J. M. H. Campbell, and J. R. B. Hern: Gastric Secretion, Plasma and Physical Fitness. *Guy's Hosp. Rep.*, 74:339, 1924.  
 Bell, J. R., and W. MacAdam: The Variations in Gastric Secretion of the Normal Individual. *Am. J. Med. Sc.*, 167:529, 1924.  
 Bennett, T. L., and J. A. Kyle: Studies in Gastric Secretion. V. A Study of Normal Gastric Function Based on the Investigation of One Hundred Healthy Men by Means of the Fractional Method of Gastric Analysis. *Guy's Hosp. Rep.*, 71:286, 1921.  
 Bloomfield, A. L.: Clinical Aspects of Gastric Secretion. *Ann. Int. Med.*, 6:167, 1932.  
 Bloomfield, A. L., and W. S. Pollard: The Diagnostic Value of Studies of Gastric Secretion. *J. A. M. A.*, 92:1505, 1929.  
 Bloomfield, A. L., and W. S. Pollard: Gastric Anacidity, The Macmillan Co., New York, 1933.

- Crohn, B. B., and J. Reiss: Studies in Fractional Estimations of Stomach Contents. *Am. J. Med. Sc.*, 154:867, 1917.  
 Kopeckoff, N.: Individual Variation as Influencing Refractory Fractional Method of Gastric Analysis. *J. A. M. A.*, 78:404, 1922.  
 Lyon, B. B. V.; H. J. Bartle, and R. T. Ellison: Clinical Gastric Analysis with Detail of Method and a Consideration of the Maximum Information to be Obtained. *N. Y. Med. J.*, 114:272, 1921.  
 Refruss, M. E.: Diagnosis and Treatment of Diseases of the Stomach with an Introduction to Practical Gastro-Enterology. W. B. Saunders Co., Philadelphia, 1927.  
 Van Zant, F. R., and W. C. Alvarez: What is the Value of One Gastric Analysis? A Study of the Daily Variations in the Gastric Acidity of Two Normal Persons. *Proc. Staff Meet. Mayo Clin.*, 6:119, 1931.

## Studies on the Relation of Non-Specific Ulcerative Colitis to Bacillary Dysentery (with Particular Reference to the Dysentery Bacteriophage)\*

By

A. WINKELSTEIN, M.D.

and

C. HERSCHBERGER

NEW YORK CITY, NEW YORK

IN a recent discussion of non-specific ulcerative colitis (1) it was concluded that neither the cause nor the cure of this disease has satisfactorily been demonstrated. Therefore, we have been carrying on in recent years some special bacteriologic, immunologic, and therapeutic studies in patients affected with non-specific ulcerative colitis. Because of the opinion expressed by Hurst (2), Strauss (3), Crohn (4), Thorlakson (5) and others that the disease is acute or chronic bacillary dysentery, we have turned our attention to that possibility. In this communication, only studies on the relationship of bacillary dysentery to non-specific ulcerative colitis will be presented.

### BACTERIOLOGIC STUDIES

**Method I.**—The scrapings from the mucosa were placed in meat infusion broth pH 7.4. The broth culture was then streaked out on five Endo plates. After incubation at 37° for 24 hours the non-lactose fermenting colonies were in-

oculated into sugars, i.e., lactose, saccharose, glucose, maltose, and mannite. Micro-organisms showing sugar reactions characteristic of *B. Dysenteriae* were agglutinated with five different types of anti-dysentery serum i.e., Shiga, Flexner, Mt. Desert, Hiss and Sonn .

Routine cultures were taken through the sigmoidoscope directly from the mucous membrane lesions. In many instances the mucosa was first scraped and then the culture taken and in some cases biopsy specimens were cultured. Also repeated cultures were taken from fresh stools. These cultures demonstrated the following organisms from the ulcerated areas (Table I): in 60 consecutive cases studied, *B. coli* was present in all; in 26 cases *B. coli* predominated; in 23 cases *B. coli* and *Enterococcus*. *B. Alkaligenes*, *B. Friedlander* and the various strains of streptococcus (*alpha*, *beta* and *gamma*) were only occasionally encountered. Apparently the bacteria found in ulcerative colitis stools are those usually encountered in stools of normal individuals. It is of course possible that special strains of

\*From the Laboratories of the Mount Sinai Hospital, New York City.  
 Received May 21, 1934.

TABLE I

| No. of Cases | B. Coli | Enterococcus | B. Alkali-genes | Strep. Hemolyticus | Strep. Non-Hemolyticus (Indif. Gama) | Strep. Non-Hemolyticus (Vir. Alpha) | B. Friedlander |
|--------------|---------|--------------|-----------------|--------------------|--------------------------------------|-------------------------------------|----------------|
| 26           | +       |              |                 |                    |                                      |                                     |                |
| 23           | +       | +            |                 |                    |                                      |                                     |                |
| 3            | +       | +            | +               |                    |                                      |                                     |                |
| 1            | +       |              |                 |                    |                                      | +                                   |                |
| 1            | +       |              |                 |                    | +                                    |                                     |                |
| 2            | +       |              |                 |                    |                                      | +                                   |                |
| 4            | +       |              |                 |                    |                                      |                                     | +              |

Bacteriology of the stools in 60 cases of ulcerative colitis.

these organisms are involved. Anaerobic studies were not carried out. In 7 cases which were considered clinically typical instances of chronic non-specific ulcerative colitis, strains of bacillary dysentery organisms (1, Shiga; 3, Flexner, and 3, Mt. Desert) were isolated and confirmed by agglutination tests.

In addition to the 7 cited above, 20 other cases were encountered in 120 consecutive ulcerative colitis patients with a positive agglutination of laboratory strains of dysentery organisms by the serum of the patient. In these cases, agglutinins for the Flexner, Mt. Desert, Hiss, Sonnè, and Shiga strains appeared in dilutions of 1:80 to 1:1280. (See Table II). In a very comprehensive survey of what may be considered the normal agglutination *titer* for the various strains of dysentery organisms, Lentz and Prigge (6) arrived at the following conclusions: (1) For the Shiga strain, normals are either negative or range from 1:20 to 1:40. A *titer* of 1:50 is necessary for diagnosis. (2) For the Sonnè strain, even 1:20 is sufficient for diagnosis. (3) For the Flexner strain, normals may demonstrate agglutinins in dilutions of 1:50 to 1:80. These authorities consider 1:100 necessary for the diagnosis of Flexner dysentery. Accepting their conclusions, 3 of our cases who had a *titer* less than 1:100 may be considered questionable. It is also possible that agglutinins in some cases of bacillary dysentery are present only for the homologous or harbored strain of dysentery organisms. Of course, it is well known that agglutinins may disappear rapidly or may not appear, or appear late and disappear rapidly, hence they may be missed very easily.

Apparently careful bacteriologic and serologic studies will reveal that some cases of non-specific ulcerative colitis are indeed true epidemic bacillary dysentery, more or less chronic in nature. Recently, on the

TABLE II

| Cases | Flexner                                                               | Shiga   | Mt. Desert                               | Sonnè  | Hiss    |
|-------|-----------------------------------------------------------------------|---------|------------------------------------------|--------|---------|
| 12    | 1 : 40 (1)<br>1 : 80 (2)<br>1 : 160 (5)<br>1 : 320 (3)<br>1 : 640 (1) | 1 : 50  | 1 : 40<br>1 : 80                         |        |         |
| 1     |                                                                       | 1 : 640 |                                          |        |         |
| 4     |                                                                       |         | 1 : 80<br>1 : 160<br>1 : 320<br>1 : 1280 |        |         |
| 1     |                                                                       |         |                                          | 1 : 80 |         |
| 1     |                                                                       |         |                                          |        |         |
| 1     |                                                                       |         | 1 : 80                                   |        | 1 : 160 |

Agglutination of various strains of *B. Dysenteriae* with the serum of 10 cases of ulcerative colitis.

basis of cultural and agglutination studies Bargaen (7) has denied this possibility.

### BACTERIOPHAGE STUDIES

In view of the almost constant findings of bacteriophage in the stool of convalescent bacillary dysentery cases (D'Herelle), the idea occurred to Gregory Schwartzman to examine the stools of colitis patients for the presence of an anti-dysentery bacteriophage. Such studies have been carried out by the authors of this paper in 41 cases of non-specific ulcerative colitis (Table III).

*Method III.*—One loopful of stool was inoculated into 100 c.c. of meat infusion broth pH 7.4. After incubation for 24 hours at 37 degrees the broth culture was centrifuged at high speed and the supernatant fluid filtered through a Seitz filter. One half of 1 c.c. of the filtrate was added to the first of a series of 6 tubes containing 4.5 c.c. of meat infusion broth. The contents of the first tube were thoroughly mixed and 0.5 c.c. of the mixture carried over to the second tube. This was repeated for the third and fourth tubes, using a new sterile pipette with each tube.

TABLE III

*Dysentery Bacteriophage in the Stools of Fifteen Patients*

| Cases  | Flexner | Shiga | Hiss | Mt. Desert | Sonnè |
|--------|---------|-------|------|------------|-------|
| G. N.* | +       |       |      |            |       |
| C. S.* |         | +     |      |            |       |
| R. P.  | +       |       |      |            |       |
| F. P.* |         |       | +    |            |       |
| D. S.* | +       | +     | +    |            | +     |
| R. G.  |         | +     | +    | +          |       |
| G. A.* |         |       | +    |            |       |
| F. N.* |         | -     |      |            |       |
| K. V.* |         | +     |      |            |       |
| B. L.  |         | +     | +    | +          | +     |
| F. K.  |         |       |      | +          |       |
| T. R.  |         | +     |      |            |       |
| G. W.  | +       |       |      |            |       |
| N. B.  | +       |       |      |            |       |
| E. C.  | +       |       |      |            |       |

\*In these patients, the bacteriophage appeared in the stool as they were recovering and disappeared when they were well.

One-tenth c.c. of a 24 hour broth culture of one of the strains of *B. Dysenteriae* was added to each of these four tubes. One half of 1 c.c. of filtrate was added to the fifth tube as a bacteriophage control and 0.1 c.c. of the broth culture of the *B. Dysenteriae* strain to the sixth tube as the micro-organism control. The tubes were incubated for 24 hours at 37 degrees C. The above described titration was carried out against each of 5 strains of *B. Dysenteriae*, i.e., Shiga, Flexner, Mt. Desert, Hiss and Sonnè. The presence of bacteriophage was indicated by the appearance of lysis in one or more of the first four tubes containing the specific strain.

From these studies, it is apparent that in 15 cases out of 41 (36%) a bacteriophage, active against one or more of the laboratory strains of dysentery organisms, was found. In a certain number of cases, the stools repeatedly were examined for bacteriophage throughout the course of the disease. In 7 cases the bacteriophage was absent during the acute stage of the disease, appeared during the convalescent or recovery period, and disappeared when the patient was entirely well. In 2 cases the bacteriophage which had disappeared on recovery from a previous attack again appeared during a second attack of the disease. Only 3 cases with bacteriophage in the stools had dysentery agglutinins in the serum. Control studies on the bac-

bacteriophage were made on the stools of 45 patients who were suffering from miscellaneous diseases other than non-specific ulcerative colitis. Several cases of diarrhea from other causes (amoebic dysentery, pancreatic insufficiency, Graves' disease, functional diarrheas) were also studied. A dysentery bacteriophage was not found in any of these 45 cases.

It is very interesting to note that in a small epidemic of bacillary dysentery where 21 sick members of 4 families were studied in The Mount Sinai Hospital (the features of this small epidemic will be reported elsewhere) and in whom the diagnosis was confirmed by the finding of the Flexner strain, 10 of these patients, when convalescing, also developed in the stools a bacteriophage potent against dysentery organisms and lost it when well.

Recently, Feemster (8) reported similar findings in an epidemic of 100 cases of Hiss bacillary dysentery. He found the Hiss organisms only in 5.6% of the cases, whereas, the active bacteriophage was demonstrated in the stools of 80% of the cases. None was found in controls. He concluded, as we also believe, that the detection in the stool of a bacteriophage active for the bacillus causing the dysentery seems to be a valuable procedure for determining the etiology of cases of diarrhea.

In view of the finding of the bacteriophage in these epidemics of proved bacillary dysentery, and considering its absence in a fairly large group of controls and other diarrheas of known etiology, the demonstration of an anti-dysentery bacteriophage in 36 per cent of a series of 41 cases of non-specific ulcerative colitis seems to have some significance.

### INTRADERMAL TESTS WITH TOXINS

A further attempt to ascertain whether some cases of non-specific ulcerative colitis were bacillary dysentery was directed as follows:

Utilizing the exotoxins of stock Shiga and Flexner dysentery organisms, skin tests in the manner of the Schick tests were carried out in patients with ulcerative colitis and in controls. The toxins were prepared by growing the Shiga and Flexner stock-organisms on solid culture media and then centrifuging and filtering the saline washings. The toxins were tested in rabbits using the "Shwartzman phenomenon." A tenth of a cubic centimeter of a 1:5 dilution in saline was injected intradermally in the patients and the site inspected 24 hours later. A central area of deep red or reddish-purple induration surrounded by a zone of 2-5 centimeters of erythema was considered positive. The findings are represented in Table IV.

TABLE IV

|                    | No. of Patients | Toxin   | Positive | Negative |
|--------------------|-----------------|---------|----------|----------|
| Ulcerative Colitis | 19              | Shiga   | 14 (73%) | 5 (27%)  |
|                    | 4               | Flexner | 3 (75%)  | 1 (25%)  |
| Controls           | 19              | Shiga   | 25 (69%) | 11 (31%) |
|                    | 45              | Flexner | 15 (52%) | 3 (15%)  |

Skin tests with dysentery toxins in ulcerative colitis patients and controls.

Apparently, the percentage of positive skin tests (indicating an absence of a neutralizing antitoxin) and negative skin tests (indicating the presence of sufficient antitoxin) in patients with non-specific ulcerative

colitis is approximately the same as in the controls. However, this negative study is inconclusive. It seems necessary to carry out such skin tests using toxins of the various strains of dysentery organisms during the acute stage, during the convalescent period and in the period of complete recovery. Should these skin tests show a changing dysentery antitoxin content of the blood and if this is confirmed in rabbits using the "Shwartzman phenomenon," it would offer additional evidence that the cases of ulcerative colitis showing this sequence of events are really bacillary dysentery. Such a study is being carried out on the colitis patients.

### SUMMARY

Summarizing these studies on the relationship of non-specific ulcerative colitis to bacillary dysentery, it seems permissible to state (1) that a small number of patients affected, presumably, with non-specific ulcerative colitis, have definitely been proved to have bacillary dysentery by the finding of *B. Dysenteriac*, according to method described above.

(2) The finding of a bacteriophage active for one or more strains of bacillary dysentery organisms in 36% of one series of 41 cases of non-specific ulcerative colitis is indirect but suggestive evidence that the patients have had or are suffering from bacillary dysentery.

(3) The positive dysentery agglutinations in high titer in 27 cases is strongly suggestive. The negative instances are, as already pointed out, for various reasons, inconclusive.

(4) Only 3 cases revealed simultaneously a bacteriophage in the stools and agglutinins in the blood serum. If their etiologic significance is accepted, this would indicate that the finding of either is helpful in establishing the diagnosis of bacillary dysentery.

(5) The relation of the intradermal tests with the toxin of the dysentery organisms to the antitoxin content of the blood during the course of the disease requires further investigation.

### THERAPEUTIC IMPLICATIONS

1. *Serum.* The therapeutic implications of these studies are clear. Hurst (2), Crohn (4) and others advocated the use of polyvalent anti-dysentery horse sera in the treatment of non-specific ulcerative colitis. The results in the cases treated by us were not very striking. There are several possible explanations for this failure, viz. (a) The cases may not have been bacillary dysentery. (b) The mode of administration (25 to 50 c.c. b.i.d. intramuscularly) both as to quantity (150 c.c.) and location (intramuscular) may not have been ideal. Perhaps larger doses, 300 to 400 c.c., given intravenously in a short period of time (48 hours) may give better results. Two cases, both patients with bloody diarrhea for one year and with the typical sigmoidoscopic and radiographic findings of ulcerative colitis, were treated with 300 c.c. of anti-dysentery serum given intravenously within 48 hours with excellent results. (c) The serum may not be potent. Some batches of commercial sera did not reveal agglutinins or antitoxin. Occasionally, as mentioned, a favorable response to anti-dysentery serum therapy is seen. This is indicated by a rapid drop in the temperature, an improvement in the general condition of the patient, a lessened number of stools with a more solid consistency, and a healing of the mucous membrane as evidenced by the sigmoidoscopic and



radiographic picture. Such an improvement may be (1) specific (2) non-specific (foreign protein shock?) or (3) coincidental improvement. It is indeed very difficult to draw conclusions as to the efficacy of therapeutic measures in a disease which has, as one of its characteristic features, sudden spontaneous remissions. Improved agglutinative and antitoxic polyvalent antidysentery sera are being prepared in this laboratory for further clinical trial.

2. *Bacteriophage*. It seems logical to use bacteriophage therapy in this disease. We have utilized a polyvalent dysentery bacteriophage which is powerfully lytic against the following laboratory strains of dysentery organisms: Flexner, Shiga, Hiss, Mt. Desert, and Sonn  strains. In a group of cases, from one to three ounces of this bacteriophage solution has been instilled daily into the rectum as a retention enema following a one per cent bicarbonate of soda enema. Some patients have improved while undergoing this therapy but since the instillations were carried out for weeks, during which time a spontaneous improvement may have occurred, it is not permissible to draw a conclusion as to the therapeutic value of this procedure.

3. *Active Immunization*. An attempt to actively immunize the patients with increasing doses of dysentery toxin is now being made.

## CONCLUSIONS

1. In a small number, 7 out of 60 typical cases of non-specific ulcerative colitis, the organisms of bacillary dysentery have been found.

2. A bacteriophage potent against one or more strains of dysentery organisms was present in the stools in 15 (36%) of 41 cases of non-specific ulcerative colitis. Miscellaneous controls and other diarrhea cases (a total of 45 cases) did not reveal a dysentery bacteriophage in the stools.

3. In 27 (22%) out of 120 non-specific ulcerative colitis patients there was a positive serum agglutination for dysentery organisms.

4. Intradermal tests in ulcerative colitis patients with dysentery toxin gave approximately the same per cent of positive and negative results as did normal controls. This question requires further study.

5. The therapeutic implications of these studies, particularly the use of anti-dysentery sera and bacteriophage, are discussed.

6. These studies strongly suggest further work on the etiologic r le that bacillary dysentery may play in some cases of non-specific ulcerative colitis.

## ACKNOWLEDGEMENT

This work was aided by a grant from Mr. Herbert Salomon to whom grateful acknowledgement is made.

## REFERENCES

1. Winkelstein, A.: *N. Y. State Jour. of Med.*, Nov. 15, 1931.
2. Hurst, A.: *Proceedings of the Royal Society of Medicine*, 20:370, 1926.
3. Strauss, H.: *Deut. Med. Woch.*, No. 36, 1915.
4. Crohn, B. B.: *Transactions of the Section in Gastro-enterology of the A. M. A.*, 1927.
5. Thorlaksen, P. H. T.: *Jour. of Cand. Med. Asso.*, 19:656, Dec., 1928.
6. Lentz, O., and Prigge, R.: *Handbuch der Pathogenen Mikroorganismen* (W. Kolle and A. V. Wasserman), Vol. 3, Part 2, p. 1460.
7. Birger, J. A.; Copeland, M. C., and Buie, L. A.: *The Practitioner* CXXXVII, 235, Aug., 1931.
8. Feemster, R. F.: *Jour. Infect. Dis.*, 55:190, Sept.-Oct., 1934.

# ABSTRACTS

EDWARD S. EMERY, JR., AND ROBERT T. MONROE, M.D.,  
Boston, Mass.

*Peptic Ulcer, Nature and Treatment. Based on a study of 1435 cases. Arch. of Int. Med.*, Vol. 55, No. 2, Feb., 1935, p. 271.

The writers present an analysis of 1435 cases and have come to the following conclusions:

1. The nature of the disease is fundamentally unknown.
2. It occurs only in the regions of the gastro-intestinal tract, which are in contact with the hydrochloric acid.
3. It is essentially a chronic disease, and the factors influencing relapse are: emotion, fatigue and infections elsewhere in the body.

In 500 of this group, remissions occurred spontaneously in 131 patients. The usual length of such remissions being weeks to a few months. In 161 death ensued, due to hemorrhage in 20, perforation 28, obstruction in 4, and associated diseases in 35.

Peptic Ulcer does not tend to shorten the victim's life, the average age of death in 87, who died, was 59 years, which is the life expectancy for the general population.

32% of the patients treated medically had few symptoms thereafter. An almost equal number were moderately improved, and about 5% to a minor degree. About 13% showed that the treatment definitely failed. Thus about 81% of the patients responded in a favorable way to the medical treatment. A comparison of the medical and surgical treatment showed an appreciably higher percentage of continuous relief, but that surgical failures more than doubled the medical failures. Jejunal ulcers

followed in about 11% of the Gastro-Enterostomies. In 12% of the Gastro-Enterostomies with resection of the pylorus or a portion of the stomach. In 23% of those in which there was excision of the ulcer and in 16% of transsection of the pylorus, in which jejunal ulcers perforated into the colon, producing gastro-colic fistula.

The necessity of following up medical care with the avoidance of fatigue, infection and more careful attention to general hygiene is emphasized, as there is a tendency to over-emphasize the results secured by surgery. The maintenance of a rigid schedule is still a most important factor following operative procedure. The posterior gastro-enterostomy proved as effective an operation as excision of the ulcer. Removal of the antrum on the basis that it possessed a hormonal secretion which would decrease the Hydrochloric Acid has been shown to be an error.

The successful treatment has been based on recognition on thorough examination of other diseased conditions and their effective treatment. Emphasis on the chronic nature of the disease, with frank explanation to the patient for his intelligent cooperation, rest and diet form the basis of the treatment. The diet must meet all of the necessary requirements, with an avoidance of roughage, condiments, alcohol and tobacco. A modified Sippy plan of treatment the Authors considered was still the most successful.

Their attitude towards peptic ulcer located in the stomach is that the patient requires stay in the hospital for three weeks, under the required schedule of treatment. Then the Roentgenographic studies were repeated, and if these show no healing as compared with the first exami-

nation. Immediate operation is advised. If healing is definite, and the ulcer crater smaller, medical treatment is continued and frequent X-ray studies are made over a period of one year.

The therapy of the peptic ulcer case with obstruction, occurring in 167 of their cases, brought out the fact that there was agreement as to the clinical and Roentgenological evidence in 141 of the cases, that is there was a large residue present. Medical treatment was effective in only 28% of the cases where there was definite obstruction and a large residue. It helped in those cases in which the X-ray alone suggested obstruction. Surgical treatment produced the best result where there was a high grade of obstruction present. It seemed from their evidence, it was worth while to treat the obstruction case for a short time in a medical manner.

Hemorrhage occurred in 384 of their patients at some time. There was no way to determine which case would bleed. In 95% of the cases the bleeding stopped spontaneously, which leaves a small group in which surgery may be necessary. The performance of a surgical operation does not avoid the incidence of further hemorrhage. Of 155 patients who received surgical treatment, 17% had further hemorrhage following the procedure.

The acute perforation is definitely surgical at once. Perforation occurred in 111 of this group, and the simplest surgical procedure at this time seems to be the most reliable way of treating them, and simple closure with or without gastro-enterostomy has proved most effective.

A. H. Aaron, Buffalo.

MACMILLAN, A. S.

*Statistical Study of Diseases of the Oesophagus. S., G. and O., Vol. 60, No. 2A, Feb. 15, 1935, pp. 394-402.*

The author reviews 1600 cases in which the patient sought relief from dysphagia or some other symptom relative to the passage of food from the mouth to the stomach. Very careful X-ray examinations were made with the patients, following thin and thick barium preparations.

Foreign bodies were found in 181 cases. More than 90 per cent of the foreign bodies were found in the pyriform sinuses or the upper one-third of the oesophagus. The types of foreign bodies found in these cases were, in order of their frequency of occurrence: chicken bones, fish bones, open safety pins, small lead toys, pieces of wood, glass and a variety of hardware.

In 350 cases the cause of the dysphagia was found to be a malignancy. The ages ranged from 30 to 78 years; men predominated over women 6 to 1. In this series malignancy occurred in the oesophagus as follows: upper third, 124 cases; middle third, 103 cases; lower third, 132 cases.

Cardiospasm was found in 135 cases. Radiological examination reveals typical findings. Mosher has definitely proved that in cardiospasm there is a fibrosis and degeneration of the muscle of the oesophagus with a stenosis and secondary twist due to the dilatation and elongation of the oesophagus. The ages varied from 16 to 68 years; women predominated over men 3 to 1.

In 96 cases there was a fusiform narrowing of the upper portion of the oesophagus. The symptoms of such narrowings is the inability to swallow a large bolus of food. Treatment is practically unavailing, but the passage of bougies is reassuring to the patient.

The next most frequent cause of dysphagia was found to be the formation of partial diaphragms of mucous membrane, or webs, with central or eccentric openings. They usually follow trauma, or ulceration of the pharynx and mouth. They frequently occur opposite a cervical exostosis. The Roentgenological picture is diagnostic. Spectacular relief can be given by rupturing the thin diaphragm with instruments. This condition was found in 114 patients.

Extrinsic causes of dysphagia occurred in 31 cases. Metastatic carcinoma in the glands of the neck, and medi-

astinal tumors, present the most difficult diagnostic problems.

Burns of the oesophagus and their resulting strictures were found in 40 cases. Such strictures are usually located in the middle of the oesophagus.

Paralysis of the oesophagus was not found, but paralysis of the muscles of deglutition was noted in 46 patients. The paralysis is always of central origin and may be due to any one of several etiological factors: an infection such as poliomyelitis, a localized central hemorrhage, brain tumor, fracture of the skull, and Parkinson's disease.

Pouches of the oesophagus are rarely recognized during life because they do not produce obstruction. They are discovered during a routine examination, or at autopsy.

Pharyngeal diverticula were found in 32 cases. The ages varied from 45 to 83 years. Males predominated over females 4 to 1. The diagnosis is readily made by X-ray. The treatment is surgical elimination of the diverticulum.

Ulcers of the oesophagus were found in patients. It occurred most commonly in the lower part of the oesophagus. Substernal pain and dysphagia were the most common symptoms. X-ray findings are characteristic.

Nelson M. Percy, Chicago.

ROZENBAAL, HENDRIK M.; COMFORT, MANDRED W., AND SNELL, ALBERT M.

*Slight and Latent Jaundice. J. A. M. A., 140:374, Feb. 2, 1935.*

A study was made to determine the meaning of a slight increase in the value of the serum bilirubin and the true meaning of the indirect van den Bergh reaction. An analysis of 214 cases showing an indirect van den Bergh reaction and a serum bilirubin of 2.0 mg. per hundred cubic centimeters or above comprised the study.

Evidence of hemolytic disease was present in seventy-six cases.

The authors feel that in those cases in which there is no hemolytic disease present increased serum bilirubin means hepatic dysfunction. Also in those cases where hemolytic disease is present and excessive hemolysis is the accepted explanation of the increase in serum bilirubin, the almost universal presence of some hepatic injury suggests that it may also be partly responsible for the elevation of the bilirubin concentration.

That the indirect van den Bergh reaction does not rule out hepatic injury is maintained by the authors who have seen the van den Bergh reaction change from direct to indirect during convalescence from hepatic injury while an elevated serum bilirubin was still present.

Another interesting finding the authors mention is the fact that some patients who complain of being bilious actually have slight hepatic dysfunction.

The secretion of bilirubin is a sensitive mechanism. Emotion, disturbances in the sympathetic nervous system, as well as minor degrees of hepatic injury may influence this mechanism.

Francis D. Murphy, Milwaukee.

WINKELSTEIN, ASHER.

*Peptic Esophagitis. J. A. M. A., 104:906, March 16, 1935.*

The author presents five patients, all elderly men complaining of dysphagia, substernal pain, heartburn, and sour eructations. In three of the cases, duodenal ulcer was present, in the fourth case a peptic ulcer of the esophagus had been present previously, and in the fifth case a gastric ulcer developed subsequently. All cases showed hyperchlorhydria. Esophagoscopy was done and biopsy specimens were obtained in all cases to rule out suspected carcinoma of the esophagus. The biopsy reports were "acute and chronic purulent inflammation."

Ulcer therapy with employment of antacids gave prompt relief in all cases.

Exacerbations and remissions resembling those seen in peptic ulcer tend to occur.

Francis D. Murphy, Milwaukee.

## SECTION II—*Experimental Physiology*

### The Pancreas and General Metabolism\*

#### A Physiological, Metabolic and Philosophical Concept of Nutritional Unity and Interdependence

By

W. N. BOLDYREFF, M.D.†  
BATTLE CREEK, MICHIGAN

THE report falls into two parts: 1. Metabolism in the whole organism and 2. Metabolism in the separate cell.

##### 1. *Metabolism in the Whole Organism.*

When we discuss metabolism in connection with the function of the pancreas we involuntarily think of carbohydrate metabolism long ago studied and described in detail by the great Claude Bernard, then Minkowski and finally by many other French, German, English, Italian, American and Russian investigators. We recall also the more recent work of Macleod, Banting and their associates dealing with insulin which has so much relieved the suffering mankind in the struggle against diabetes mellitus. From this angle we shall discuss metabolism in the whole human and animal organism and the rôle of digestive hormones. But I am going to describe the relationship of the so-called external pancreatic secretion to the general metabolism.

If the introduction of the conception 'hormone' were necessary and useful in the past, it is now not infrequently abused. Hormones have so multiplied in recent years as to create much confusion in the study of physiology. Some substances are classed as hormones without having been sufficiently studied so that their content and action are fully understood. Physiology is thus turned into *philology*—no new facts, no explanations, but simply new words.

Even with the finely studied hormone, insulin, the ground is not perfectly sure.

Recently Ephraim Boldyreff (Pavlov Physiological Institute and University of Michigan) has established that (1) the amount and distribution of islet tissue in the pancreas apparently do not have any relation to the blood sugar; (2) the effect of insulin upon the digestive system invariably precedes its hypoglycemic action, and (3) insulin affects carbohydrate metabolism through the nervous system (Report to this Congress).

The newest findings on the duodenal hormone, similar to insulin, and found by the American doctors A. B. Maccallum and N. G. Laughton, also shake the faith in the specific action of insulin as a product of the islands of Langerhans, as well as the fact that many

authors have obtained insulin, or a substance similar to it in physiologic action, from various bodily organs and even from plants (Collip).

Further, a whole series of laboratory investigations and clinical observations have shown that insulin affects not alone the carbohydrate metabolism as was formerly believed, but the fat (Bloor) and the protein metabolism as well. Hence the conclusion that our views on the physiological effect of insulin, which seemed so definite, simple, and well founded, must undergo revision. Therefore (1) insulin in reality is not 'insulin' at all, i.e. it is not restricted to the islands of Langerhans, but found in the whole body of the pancreas; (2) moreover, it has other effects than upon carbohydrate metabolism inasmuch as it influences also the metabolism of other substances; (3) that, as is accepted for typical hormones, insulin acts not directly on carbohydrate metabolism but through the nervous system. (For details see the works of E. Boldyreff and others).

The correctness of this view is also confirmed by some earlier work: for instance, by the fundamental and original work of de Dominicis in Italy on the influence of pancreatic juice (so-called external secretion) on the metabolism, and also my work on the same subject supplying new data and offering new explanations, first reported at the VI Congress at Brussels (in 1904) and later described in detail in *Ergebnisse der Physiologie* in 1911 and 1929 and elsewhere.

The term 'external' secretion for pancreatic juice secreted into the intestine in distinction from a supposed, though never seen and not proven 'internal' pancreatic secretion, entering directly into the blood, is unfortunate and incorrect. In former times it would perhaps serve to describe the secretion of pancreatic juice outside in animals with pancreatic fistulae. But this term should now be abandoned in order to avoid harmful and even dangerous confusion in conceptions, since it has been proven that normally this secretion is soon absorbed into the blood and thus becomes *internal*. My experiments and those of my associates have shown that in man and vertebrate animals, when hungry, there is an abundant, regular and uniform periodical secretion of pancreatic juice into the intestine about every 1 or 2 hours (described in detail by me elsewhere). In 24 hours there are from 5 to 10 such "secretion periods" depending upon the subjects diges-

\*Reported at XIV Internat. Physiol. Congress in Rome, Aug. 30, 1932. and at Mechnikoff's Medical Society in Paris, Oct. 27, 1932.

†Director of Pavlov Physiological Institute of the Battle Creek Sanitarium.

Submitted February 12, 1935.

tive activity. The more time there is taken up by digestion, the less there is left for the periodical secretion, just as the longer the night, the shorter the day.

The periodically secreted pancreatic juice, or rather its ferments, are immediately absorbed from the intestine into the blood where the proteolytic ferment is detected by means of Abderhalden's reaction (work of Dr. Kniazoff in my Laboratory). The glucolytic (work of E. Boldyreff in my Laboratory) and lipolytic ferments are also detected by other fitting and generally known methods. Prawdich-Neminsky in Russia noticed a similar periodical appearance of catalase in the blood simultaneous with the above named ferments.

E. Boldyreff in my Laboratory has proven in his published experiments that pancreatic juice in general, both the portion secreted on food and the periodically secreted portion, possesses a glucolytic action. He has also established that the sugar content in the blood of a living being falls during the periodical pancreatic secretion and rises in the absence of it. I do not doubt that such pancreatic juice is the main source of insulin. The pancreatic juice secreted in digestion possesses the same property.

According to our data, the ferments of the pancreatic juice always, though periodically, enter the blood in the absence of digestion and during it and then are carried throughout the organism to supply the needs of all the organs, tissues and cells of the body. The general metabolism—carbohydrate, protein and fat—is effected with the aid of these ferments. They supply the energy for the functions of the body and the chemical work in the organism, under constant and exacting control of the nervous system. The importance of them was first indicated and studied by Claude Bernard and later insistently stressed by E. Pfeuger.

The correctness of the theory presented is confirmed by the following considerations.

(1) There is a parallelism between the work of the digestive organs and the general life processes in the organism. In the young organism with good digestion, there is rapid growth, quick recovery from injury or disease, resistance to fatigue and so forth; in old age, the digestion is poor and all other vital phenomena are slow and dulled.

(2) In severe sickness, all the bodily forces are concentrated for the struggle against the disease; digestion is at times stopped for lengthy periods or may be inhibited (due to lack of appetite), thus permitting the digestive ferments to be mobilized for intracellular work which is more important at such times since it assists the fight against the causes of disease.

(3) If the pancreas is the mainspring of the general metabolism, then in cases of pancreatic affections or outside secretion of pancreatic juice, the metabolism is greatly unbalanced. This is precisely the case in *diabetes mellitus* and in the animals with pancreatic fistulae as well as in pregnant women with pernicious vomiting. In these cases, a pronounced disturbance of carbohydrate and other metabolism is very apparent.

In *diabetes mellitus* we often observe presence of gangrene, poor healing of wounds, weak resistance to infection and a generally lowered vitality of cells and tissues of the whole body. This is a consequence of the affection of the pancreas and poor supply of bodily cells by the pancreatic ferments, necessary for correct nutrition and normal life. If each cell prepared its

own ferments, affections of the pancreas would have no injurious effect on the cells of the whole body. This connection between the weakened work of the pancreas and the mentioned diseased condition of the whole body, observed in *diabetes* serves as the best confirmation of the correctness of my theory on the supply of ferments to the entire tissues and cells of the organism by the pancreatic gland.

Thus the pancreas is the chief chemical agent for all general manifestations of life in the human and animal body, as the heart is the main motor agent for the circulation and the brain for the control of coordination in the functions of all organs and adaptation to life of individuals to the surrounding conditions and environment.

## 2. Metabolism in the Separate Cell.

There are almost no definitely proven data concerning general chemical process in the cell, i.e. the phenomena of destruction and reconstruction of the proteins, fats and carbohydrates. We must therefore rest satisfied with hypotheses. There is no doubt, however, that the chemical processes in the cell depend upon the work of the ferments similar to that which takes place in the digestive tract during digestion; in other words, assimilation and dissimilation of protein, carbohydrate and fat, both in the cell and in the digestive tract, are effected by the same agents.

Claude Bernard said: "Ferments treasure the mystery of life." Later, Emil Fischer repeated the same thought in other words: "Wir dürfen . . . mit ziemlich grosser Wahrscheinlichkeit annehmen, dass sie (Fermente oder Enzyme, W. N. B.) bei allen Verwandlungen in der lebenden Zelle betheilt sind."

Each cell must contain all the main digestive ferments, proteolytic, lipolytic and glucolytic. Thirty years ago Professor I. P. Pavlov proved that proteolytic, digestive ferments are capable not only of splitting proteins, but also of recreating them from the split-products. Even earlier, Croft Hill, in England, found the same to be true for carbohydrate ferment, and later Kastle and Loevenhart in America found it to be true also for the fat ferment, which was also mentioned by Claude Bernard. To sum up, all these ferments possess a twofold property: to split and to reconstruct.

In the life economy of some cells (muscle cells) carbohydrates play the main part; in others, such as brain cells, the fats; and in others (cells of red blood corpuscles) the proteins. They all, however, must at times split and reconstruct all of the three basic substances which make up any living cell and which also serve as the main food for the whole organism, i.e. carbohydrates, fats and proteins.

It follows that each cell must have in it all three kinds of ferments. What is the source of supply for them? Are they made in the cell itself or borrowed from elsewhere? Only the cells of the pancreas and small intestine (perhaps also leucocytes) are capable of making all the named ferments. Even the cells of the digestive glands, which specialize in the production of ferments, are restricted to their particular product. The gastric gland cells make only pepsin; the salivary gland cells only ptyalin (in man), but neither one can make lipase or any other ferment. The less probably, then, is the assumption that the specific cells which do not participate in the elaboration of ferments, such as the muscle cell, nerve cell, kidney cell,

connective tissue cell, etc., can create for themselves all three kinds of ferments or even one of them. They are supplied to them ready made. Where is the origin of this supply?

Essentially, as stated above, the process of splitting and reconstruction of protein, fat and carbohydrate in the digestive tract and the processes of their dissimilation and assimilation in each cell are perfectly alike. Hence in both cases the same ferments are at work.

Now the main source of supply of ferments for all the bodily cells becomes clear: the main "factory" would appear to be the pancreas.

All the main digestive ferments—proteolytic, lipolytic and amylolytic—enter the blood current in profusion both during absorption of digested food and in the absence of digestion during the before mentioned phases of periodical pancreatic secretion, and are carried in the blood stream throughout the body. Thus, every cell of every organ is supplied with them. When no more useful, the ferments are cast back into the blood stream or the lymph and are either carried outside in the urine and other excretions or absorbed by the leucocytes for their own needs.

This investigation would seem to designate the pancreas as the large "factory" where ferments are being prepared for the general metabolism in the whole body. But the pancreas is not the only source of these ferments. Intestinal glands (in the small intestine), prepare a juice very similar in its properties and in ferments and their action, to the pancreatic juice and second to it only in its strength. Thus, the intestine assists the pancreas. Therefore, it is clear that removal of large sections of small intestine in various operations is not without effect on the body.

In the limited space of an ordinary report one is perforce restricted to the general points of the problem, indicating its main stages, and it is impossible to take time for discussion of even important details. I trust the reader will pardon the incompleteness and the schematic nature of this paper.

I sincerely hope that the ideas here expressed will find response in some of my readers, at least among the younger generation of physiologists whose minds are more open to the reception of new suggestions than

are those of the older generation who may be prejudiced by their interests and previous conceptions in favor of the already accepted and established theories in the field of science. Therefore again I make an appeal, as I did in 1911, to all who are interested in metabolism to apply their efforts to this so fruitful and as yet so little studied field.

## CONCLUSIONS

1. Apparently the general metabolism (carbohydrate, fat and protein) in the whole body as well as in each separate cell, is effected with the aid of certain pancreatic ferments. These ferments are being secreted in the pancreatic juice and are absorbed into the blood (and hence into the cells) during digestion and in fasting (during the periodical activity).

2. The "external" pancreatic secretion with all its ferments is quickly absorbed from the intestine into the blood, and constitutes the true "internal" pancreatic secretion which controls not only the carbohydrates, but also other metabolism. There is no other "internal" pancreatic secretion in the old sense of the word, i.e. there is no direct absorption into the blood from the pancreas of a specific substance controlling the carbohydrate metabolism, independently from the external secretion.

3. There are no endogenous ferments prepared by the cells themselves for the needs of general intracellular digestion (splitting and reconstruction of carbohydrates, fats and proteins). Only specific substances and specific ferments can be prepared in the cells of special organs (adrenalin in suprarenal glands, thyroxin in the thyroid apparatus, and so forth).

4. The pancreatic and the intestinal ferments, entering the blood very soon leave it, being absorbed by the cells and tissues of the whole body (in the liver, lungs, muscles, etc). Experiments of Ludwig's laboratory have shown that the blood loses its ferments in about 4 hours. For this reason, all digestive periodical ferments, such as pancreatic and intestinal, usually are secreted every one or two hours, otherwise the blood would become "fermentless."

5. There is evidence to support the view that the pancreas is the main agent of all general chemical processes in the organism.

## REFERENCES

1. Boldyreff, E.: New Aspect of Pancreatic Function in Carbohydrate Metabolism. *Proceedings of the XIV Intern. Physiol. Congr.*, Rome, Italy, v. 37, 1932.
2. Laughton, N. B., and Macellum, A. B.: The Relation of the Duodenal Mucosa to the Internal Secretion of the Pancreas. *Proceedings of the Royal Society B.*, Vol. 111, 1932. London, England.
3. De Dominieis: See Luciani, L., *Human Physiology*, Vol. 2, p. 99. London, 1913.
4. Boldyreff, W. N.: *Arch. Sc. Biol.*, 11, 1, 1904-1905. *Ergebn. d. Physiol.*, 11, 182, 1911. *Ibidem*, 29, 1929. Ext. and Int. Seere. Paner. and Their Interrel. *Proceedings of the XIII Intern. Physiol. Cong.*, Boston, 1929.
5. Kniazeff, I. D.: *Jour. of Neur.*, Kazan, 21, 2, 1914 (In Russian).
6. Boldyreff, E.: *Pflueger's Arch.*, 218, H. 5/6, 553, 1928.
7. Prawdich-Neminsky, W. W.: *Biochem. Z.*, 192, H. 3, 141, 1928.
8. Pavlov, I. P.: *Arch. f. Physiol.*, 452, 1887.
9. Boldyreff, W. N.: *Erg. d. Physiol.*, 29, 577-579, 1929.
10. Pavlov, I. P., and Parastschuck, W. S.: *Zeitschr. Physiol. Chem.*, 42, 415, 1904.
11. Hill, Croft: *J. Chem. Soc.*, London, 73, 634, 1898.
12. Kastle and Loevenhart: *Am. Chem. Journ.*, 24, 491, 1900.
13. Loevenhart: *Am. J. Physiol.*, 6, 331, 1902.

## SECTION III—Nutrition

### What Should be the Per Capita Per Day Milk Consumption of Our Population?

By

LLOYD ARNOLD, M.D.\*  
CHICAGO, ILLINOIS

IT is significant, and very encouraging, to note that this official publication of the American Gastroenterological Association has an important section on Nutrition. No single group of the medical and allied professions is in such an advantageous position to evaluate nutrition as members of this Association. The gastroenterologist sees more instances of maladjustment to nutritional environment than any group in medicine. Man, as well as other forms of organized protoplasmic life, must adapt himself to three major environmental influences, nutritional, meteorological and parasitic. The last is taken in its broadest sense, meaning bacteria, parasites, viruses, etc. The successful adaptation to these three factors constitutes a normal or healthy person. Maladjustment to any one leads to abnormal physiological symptoms. These three environmental or external factors are, therefore, interrelated with each other. The author (1) dealt with this subject in a previous publication. It is the purpose of this paper to mention one of our common foods, and to indicate the need of the gastroenterologist's experience and influence in aiding the public health authorities in their educational programs in nutrition.

The value of milk as a food has been established and is recognized by all students of nutrition. The public has become "milk conscious." The value of the proteins, sugar, fat, inorganic salts and the vitamins has been repeatedly and thoroughly studied by many investigators. Milk is considered as one of the almost complete foods; that is, it supplies a large number of the essential factors for nutrition.

The per capita consumption of milk in this country is said to be approximately one pint per day. Tobey (2) states that there are fifty-six gallons of whole milk consumed per person in this country per year. This would, therefore, figure out to be approximately a little less than one-half quart per capita per day. The Pennsylvania State College of Agriculture and the United States Department of Agriculture carefully investigated the whole fluid milk consumption in Philadelphia and certain suburbs in 1924, 1929 and 1934 (3). Table I is reproduced from this report. The last column of this table needs some explanation. After the investigators had ascertained the estimated milk consumption

per capita per day from each family, an accurate check was made by examining the milk dealers books who supplied this product to the families. It was found that there was usually an over estimate given the investigator by the housewife. The last column represents the deduction according to the amount of milk sold by the dealer. It was found, for instance, that during the 1934 survey, 8.3% of the 3004 families in the city of Philadelphia did not use milk and 2.9% of the 409 suburban families did not use milk. Health authorities recommend one quart per day for children up to thirteen or fourteen years of age. Milk in this country always means fluid fresh whole cow's milk. Authorities on nutrition and public health refer to the relatively large milk consumption by the population of

TABLE I  
*Comparisons of Daily per Capita Consumption of Milk for Different Nationalities. (Philadelphia)*

| Year | Native White (Pints) | Negro (Pints) | Italians (Pints) | Jewish (Pints) | All Groups (Pints) | Corrected Estimates (Pints) |
|------|----------------------|---------------|------------------|----------------|--------------------|-----------------------------|
| 1924 | 0.74                 | 0.39          | 0.42             | 0.78           | 0.69               | 0.62                        |
| 1929 | 0.84                 | 0.47          | 0.57             | 0.82           | 0.77               | 0.68                        |
| 1934 | 0.73                 | 0.45          | 0.52             | 0.72           | 0.64               | 0.60                        |

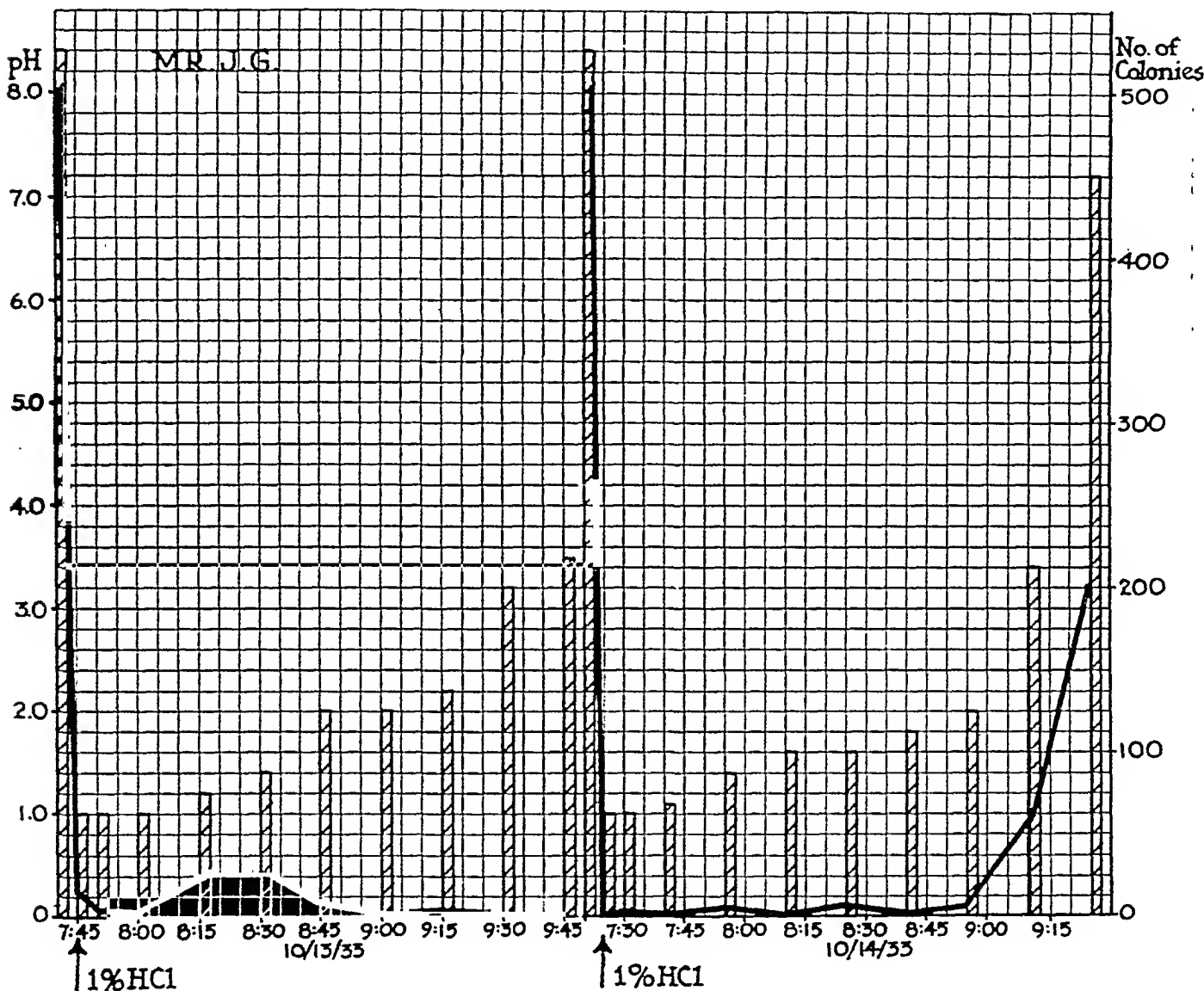
the dairy producing countries of northern Europe, such as Holland, Denmark and Finland. Tigerstedt (4) and Sundstroem (5) are most frequently quoted in this connection. The food habits of any particular folk are rather complicated when one tries to analyze the nutritional status from a purely scientific standpoint. Most of the ingredients of the diet of the peoples in northern Europe go back much further in history than can be obtained in this country. The inhabitants of many European countries have ingested a rather constant diet for many years. Sundstroem (5) has made the most painstaking survey of the actual diet ingested by a given folk over a considerable period of time. He has tabulated very carefully the diet consumed by the Finnish people in various walks of life, as well as for different age groups.

\*Professor of Bacteriology and Public Health, University of Illinois, College of Medicine, Bacteriologist in charge of the Research Laboratory of the Illinois Department of Public Health.  
Received June 16, 1937.



Table II is a reproduction of Table XII, p. 148 from Sundstroem's monograph (5). There were large enough samples in each respective age group to give trustworthy data. Table III is taken from Tigerstedt's publication (6) as the average composition of the diet of the Finnish folk. Table IV is from the Sundstroem's work (7) and deals with the ratio of milk to the total diet for the various age groups. We have compiled in

Whole cow's milk contains certain essential constituents for the rapidly growing calf. The cow in the undomesticated state ordinarily delivers her calf during the early spring. The calf is exposed to sunlight, begins eating green grass very early and supplements the milk with other food. The milk, however, contains the inorganic salts for rapid osseous tissue formation. Cow's milk, therefore, contains more alkaline sub-



Graph 1

Ordinate indicates pH and viable bacterial count of aspirated, fasting gastric contents. The continuous heavy line represents the number of viable bacteria per c.c. of gastric sample. The crossed-barred column represents the pH of the gastric samples. Abscissa indicates time. The arrow indicates the time when 100 c.c. of a 1% HCl in warm water were introduced in the stomachs through the tube. Two tests are shown on following days in the graph. Gastric contents remained acid for two hours and one hour and forty-five minutes after introduction of dilute acid. Note correlation between pH and viable gastric bacterial flora.

Table V the essential data on milk consumption from Table II from Sundstroem's work (5).

The per capita consumption of milk in Finland is, according to the above-mentioned reports, close to 1000 grams per day, divided as follows: 97.5 grams as whole milk (10%), 568 grams as skimmed milk (58.2%) and 309 grams soured milk (31.7%) making a total of 974.5 grams per capita milk ingestion. It should be noted that only ten per cent of this is fresh whole cow's milk. Almost one-third is acidified or soured milk, the remaining is defatted or skimmed milk.

stances than does human milk. Many of the feeding formulas for infants are based upon a reduction of the alkaline content of cow's milk (Arnold (6) and (7)).

It is general knowledge that adults in this country do not drink so much milk as children; this is particularly true for the older adult group. The reason may be physiological and due to changes in gastro-intestinal function with age. Friedenwald and Morrison (8); Friedenwald and Brown (9); Poeschel (10); Keefer and Bloomfield (11); Davies and James (12); Bloomfield and Kiefer (13); Pollard and Bloomfield

(14); Pierce and Bogan (15); Van Zant, Alvarez, Eusterman, Dunn and Berkson (16), and Hartfall (17) are a few of the workers who have recorded a decreasing gastric acid secretory function with advancing age. These investigators do not agree on the reasons underlying this diminished response of the gastric mucosa to physiological stimuli. Arnold (18) called attention to the influence of this hypoacidity of

be living in large numbers in the stomach, duodenum and upper jejunum, (Arnold (1)).

Arnold and Hood (19) reported observations upon the relationship of gastric acidity and viable bacteria within the human stomach. Physicians have known for many years that oral administration of acid was advantageous in aiding the correction of certain abnormal symptoms in patients with hypoacidity. The

TABLE II

*Average Composition of the Diet Expressed in Grams of the Various Foods Consumed Daily. (Sundstrom)*

|                   | Meat | Bacon | Fresh Fish | Salt Fish | Whole Milk | Skimmed Milk | Sour Milk | Butter | Fresh Bread | Dried Bread | Cereals | Potatoes |
|-------------------|------|-------|------------|-----------|------------|--------------|-----------|--------|-------------|-------------|---------|----------|
| Children 2-3 yrs. | 13   | 7     | 7          | 1         | 169        | 459          | 139       | 10     | 54          | 17          | 30      | 47       |
| 4-5 yrs.          | 18   | 12    | 10         | 3         | 72         | 317          | 272       | 14     | 196         | 1           | 14      | 197      |
| 6-7 yrs.          | 16   | 10    | 14         | 5         | 221        | 576          | 263       | 15     | 190         | 35          | 36      | 168      |
| 8-9 yrs.          | 22   | 8     | 21         | 8         | 61         | 692          | 230       | 16     | 285         | 69          | 50      | 205      |
| 10-11 yrs.        | 33   | 13    | 30         | 8         | 122        | 594          | 319       | 24     | 301         | 64          | 29      | 248      |
| Boys 12-17 yrs.   | 85   | 16    | 19         | 13        | 51         | 558          | 302       | 27     | 332         | 111         | 64      | 311      |
| Girls 12-17 yrs.  | 60   | 11    | 35         | 16        | 65         | 402          | 533       | 41     | 404         | 9           | 30      | 409      |
| Adult men         | 95   | 19    | 36         | 38        | 114        | 905          | 427       | 37     | 357         | 221         | 90      | 543      |
| Adult women       | 63   | 13    | 41         | 24        | 63         | 611          | 299       | 20     | 308         | 60          | 67      | 387      |

advancing age on the intestinal flora and the retrogressive diseases so common in this age group.

Those folk in northern, eastern and southern Europe who ingest milk in relatively large quantities do not use much whole fresh milk, but soured milk, skimmed milk and various kinds of cheeses. The physician interested in nutrition should recognize the changing pattern of gastro-intestinal secretory function with age and adjust the diet to meet the needs of such age groups.

Most gastroenterologists think of hypoacidity in terms of various abnormal physiological manifestations, due probably to interference with proper diges-

amount of acid was too small to explain the benefits enjoyed by the patient upon orthodox physiological knowledge of digestion. Arnold and Hood (19) offered an explanation for the clinical results experienced by physicians after administering dilute acid to these cases. Graphs 1 and 2 show the relationship of gastric acidity and the number of bacteria growing from one cubic centimeter of gastric contents. The administration of dilute acid by mouth gives the patient a variable time (one to three hours) of a normal gastric and duodenal bacterial flora. A person in the older age-group with a gradually decreasing gastric acid secretory power has an associated change in the bac-

TABLE III

*Average Composition of the Diet of the Finnish People Expressed in Grams Ingested Per day. (Tigerstedt)*

| Population Groups | Meat (Grams) | Bacon (Grams) | Fresh Fish (Grams) | Salted Fish (Grams) | Milk* (Grams) | Butter (Grams) | Fresh Bread (Grams) | Dried Bread (Grams) | Cereals (Grams) | Potatoes (Grams) |
|-------------------|--------------|---------------|--------------------|---------------------|---------------|----------------|---------------------|---------------------|-----------------|------------------|
| Children 2-3 yrs. | 13           | 7             | 7                  | 1                   | 607           | 10             | 54                  | 17                  | 30              | 47               |
| 4-5 yrs.          | 16           | 12            | 12                 | 4                   | 899           | 16             | 199                 | 15                  | 28              | 170              |
| 6-11 yrs.         | 25           | 14            | 27                 | 11                  | 1019          | 16             | 250                 | 58                  | 38              | 224              |
| Girls 12-16 yrs.  | 43           | 16            | 37                 | 21                  | 1115          | 42             | 424                 | 15                  | 31              | 599              |
| Boys 12-16 yrs.   | 88           | 19            | —                  | 12                  | 837           | 12             | 302                 | 122                 | 85              | 397              |
| Women Adults      | 59           | 13            | 48                 | 25                  | 913           | 20             | 329                 | 50                  | 51              | 374              |
| Men Adults        | 81           | 7             | 42                 | 45                  | 1514          | 49             | 358                 | 226                 | 128             | 652              |

\*Tigerstedt, p. 129. Whole milk, skimmed milk and sour milk included.

tion. These patients do not usually show evidence of malnutrition; many times they are well nourished or overweight. When the gastric contents are completely saturated with acid and an excess of free acid, over and above the amount needed for buffering both chemically and physically the ingested food, there are very few viable bacteria in the stomach, duodenum and upper part of the jejunum. If this does not take place, that is, the concentration of acid is not enough to completely saturate the gastric contents, then oral and ingested food bacterial flora, as well as coli-aerogenes strains from the lower intestinal levels can be found to

terial flora of his stomach, duodenum and upper jejunum. When the gastric mucosal glands secrete acid in a normal manner, that is, the hydrogen-ion is concentrated within the gastric lumen so that all the contents are acid-buffered and free acid as such exists, then the bacterial flora of the stomach, duodenum and upper jejunum is normal. Hypoacidity brings about systemic changes more by a loss of control of the bacterial flora than by an interference with hydrolysis of ingested food. It would seem that acid-buffered foods would be physiological in these cases.

Soper (20) suggests sterile milk to be fed in the

place of raw and pasteurized milk. If sterile milk is ingested it will not be sterile when it passes through the oral cavity. It will contain many more bacteria than originally present in pasteurized milk before it reaches the stomach. Arnold and Stuart (21) have

TABLE IV

*The Proportion of the Amount of Milk to the Total Diet*

|                       |          |
|-----------------------|----------|
| Children<br>2-3 years | 3.26 : 1 |
| 4-7 years             | 1.91 : 1 |
| 8-11 years            | 1.78 : 1 |
| Girls<br>12-16 years  | 0.91 : 1 |
| Boys<br>12-16 years   | 0.81 : 1 |
| Adult women           | 0.94 : 1 |
| Adult men             | 0.94 : 1 |

shown the dorsum of the tongue to have a rich endogenous bacterial flora. Next to the colon this area on the top of the tongue supports the most densely populated bacterial population we have encountered in our studies. The stomach is being constantly seeded with a variety of bacteria carried down with saliva, as well as in fluids and food. The bacteria Soper mentions in pasteurized milk are nothing to become excited about. No bacterial counts are recorded, the strains mentioned were not identified bacteriologically. He produces no evidence whatever to show the bacteria are of human origin. Pasteurized milk is safe and wholesome. Practically all the food we ingest contains bacteria. These bacteria are not superimposed upon our intestinal flora, but are killed before they become adapted to intra-intestinal conditions of life. The by-products of bacteria growing in food are the real health factors. The development of irritating chemical substances in food such as milk, by bacterial growth, is one of the reasons for low bacterial counts. The application of our tried and experienced knowledge of sanitary science plus refrigeration make pasteurized milk safe.

The fate of ingested bacteria as brought out by Hanszen (22) is of greater significance than the elimination of saprophytic air and bovine strains from food. This worker has shown, subsequent to the above mentioned publication, that when viable bacteria leave the stomach they can be found in the upper part of the large intestine several hours later. The fat content of whole milk (3.5% butter fat), the buffer value (requiring approximately equal volumes of normal gastric juice, pH. 2.0, to cause the appearance of free acid) both influence the rapidity of gastric acidification and hence allow viable bacteria to pass into the lower levels of the intestinal tract.

The most important question for gastroenterologists is not the technical and detailed problems of milk hygiene, but the directed public health movement to increase milk consumption in adults. It is taken for

granted that one quart of milk per day for the growing child is advantageous. There is some question whether a quart of fresh, whole fluid cow's milk per day for adults is advantageous. The writer knows of no population or country where this has ever been done. No experience can be cited to show this amount of whole milk ever has been consumed by a given adult population for any period of time.

The mineral elements in food required for proper nutrition make milk an outstanding product. These salts are present in all milk products except the butter-fat. Skimmed milk, soured milk and various cheeses contain the inorganic elements of whole milk, as well as do dried and condensed milk products.

Gulbrandsen and Arnold (23) are studying the *gastric response to milk and certain milk products*. The following data can be quoted here from our protocols. Two hundred cubic centimeters of whole milk (3.5% butter-fat) leave the stomach of healthy young men (18-22 years of age) in three hours and twenty-five minutes. The same amount of skimmed milk, top cream removed, (containing approximately 1% butter-fat) leaves the stomach three hours after ingestion. The aspirated samples show that after fifteen minutes the hydrogen-ion concentration had dropped from 7.2 to 4.3 after whole milk and to 1.8 after skimmed milk was ingested. The above data were obtained from eight subjects, six experiments on each subject, making an average of forty-eight experiments. The milk above was ingested into a fasting stomach. These experiments are not original in any way. The inhibitory action of fats on gastric acid secretion and the influence of fats upon the emptying-time of the stomach are well known to physiologists and gastroenterologists. The buffer values of whole and skimmed milk in *in vitro* experiments do not differ beyond the range of experimental error. This would be expected because

TABLE V

*Average Daily Consumption of Milk by the Finnish People. (Sundstroem)*

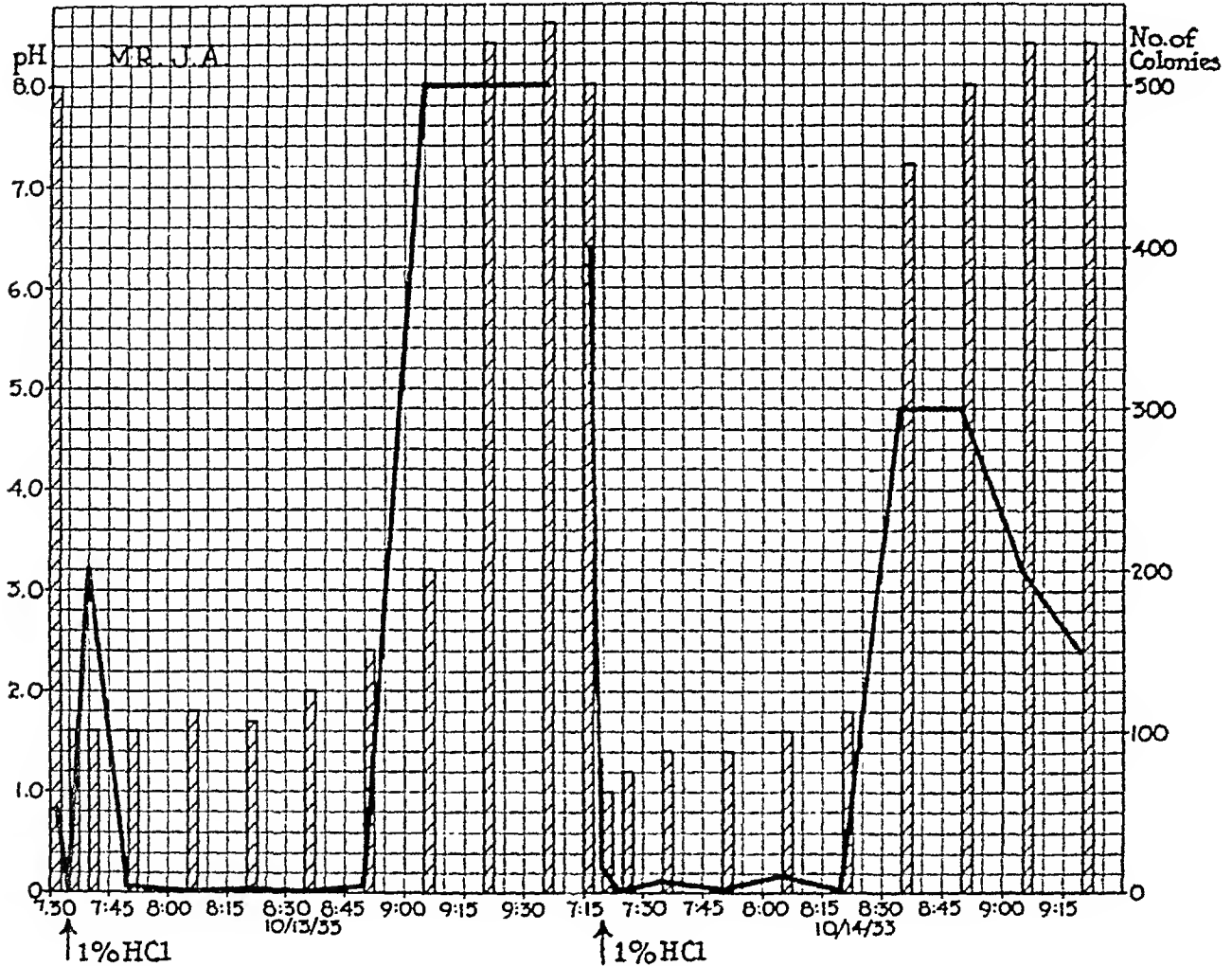
| Age Group   | Totnl Grams | Whole Milk |         | Skimmed Milk |         | Sour Milk |         |
|-------------|-------------|------------|---------|--------------|---------|-----------|---------|
|             |             | Grams      | Percent | Grams        | Percent | Grams     | Percent |
| 2-3         | 707         | 109        | 15.4    | 459          | 65.0    | 139       | 19.6    |
| 4-5         | 661         | 72         | 10.9    | 317          | 48.0    | 272       | 41.1    |
| 6-7         | 1060        | 221        | 10.7    | 576          | 54.3    | 263       | 24.7    |
| 8-9         | 983         | 61         | 6.09    | 692          | 70.4    | 230       | 23.4    |
| 10-11       | 999         | 122        | 12.2    | 558          | 55.8    | 319       | 31.9    |
| 12-17 (M)   | 947         | 51         | 5.3     | 594          | 60.4    | 302       | 31.7    |
| 12-17 (F)   | 1000        | 65         | 6.5     | 402          | 40.2    | 533       | 53.3    |
| Adult Men   | 1446        | 114        | 7.7     | 905          | 62.5    | 427       | 29.5    |
| Adult Women | 973         | 63         | 6.4     | 611          | 62.7    | 299       | 30.8    |
| GRAND TOTAL | 8785        | 878        | 10%     | 5114         | 58.2%   | 2794      | 31.9    |

of the chemical composition and reactions of the fat. The difference between the *in vivo* and *in vitro* hydrogen-ion concentration observations are due to the inhibiting action of fat on gastric acid secretion. These factors are only mentioned to indicate the complexity

of any problem involving a public health program in nutrition.

The *butter-fat content of milk* has been used for so long as the criterion of undiluted fresh whole milk that almost everyone uses the visible cream-line as an index as to the quality of the product. The butter-fat content can be determined easily and accurately, hence

vitamin B and G remain in the milk after removal of the fat. Vitamin A is widely distributed in nature, such as the fat of animal tissues as well as the liver and many leafy and tuberous vegetables. The biological significance of butter-fat resides in its vitamin A content; other than this factor it is a fuel food and can be replaced by any carbohydrate or fat.



Graph 2

Ordinate indicates pH and viable bacterial count of aspirated, fasting, gastric contents. The continuous heavy line represents the number of viable bacteria per c.c. of gastric sample. The crossed-barred column represents the pH of the gastric samples. Abscissa indicates time. The arrow indicates the time when 100 c.c. of a 1% HCl in warm water was introduced in the stomachs through the tube. Two tests are shown on following days in the graph. Gastric contents only remained acid for one and one-half hours and again for one hour and fifteen minutes after introduction of dilute acid into stomach. Note the close correlation between gastric bacterial flora and hydrogen-ion concentration.

public health regulatory boards have accentuated the popular idea of the importance of the cream content of milk. The basic reason is to prevent dilution with water, but the dairy industry has become so well organized that this safeguard against the addition of water is not so important. The bacterial count or the hygienic quality is more important now than is the fat content. The consumer, as well as the public health official and physicians, all regard the butter-fat content of major importance in fresh whole milk.

Butter-fat contains the fat soluble vitamin A;

The gastro-enterologist has a responsibility in the whole problem of the food habits of the general population. He best can correlate the theoretical, scientific and practical aspects of human nutrition. The nutritive value of defatted milk has received little attention in this country. Present economic conditions warrant giving careful thought to the diet. The per capita per day milk consumption is a subject not yet settled and one that should receive the attention of gastro-enterologists.

## REFERENCES

1. Arnold, L.: Alterations in the Endogenous Enteric Bacteria Flora and Microbic Permeability of the Intestinal Wall in Relation to the Nutritional and Meteorological Changes. *Jour. of Hygiene*, 29:82, 116, 1929.
2. Tobey, J. A.: Milk, the Indispensable Food. Olsen Publishing Company, Milwaukee, 19.
3. Certified milk, 10:7, May, 1935.
4. Tigerstedt, R.: Zur Kenntniss der Aschebestandteile in der frei gewoebten Kost des Menschen. *Skand. Arch. f. Physiol.*, 24:97, 1911.
5. Sundstroem, S.: Untersuchungen ueber die Ernnehrung der Landbevoelkerung in Finnland. Helsingfors, 1908.
6. Arnold, L.: Influence of Acidified Milk on Duodenal Function in Infants. *Amer. Jour. Dis. of Children*, 31:668, 1926.
7. Arnold, L.: Diarrhea in Infants. *Archives of Pediatrics*, 11:71, 1927.
8. Friedenwald, J., and Morrison, T. H.: The Clinical Significance of Achylia Gastrica. *Ann. Clin. Med.*, 5:319, 1926.
9. Friedenwald, J., and Brown, L. T.: Note on the Absence and Marked Diminution of the Hydrochloric Acid of the Gastric Contents in Cancer Involving Organs Other than the Stomach. *Med. Jour. and Record*, 126:491, 1927.
10. Poeschel, R.: Untersuchungen ueber die Magenfunktion bei mageregesunden alten Leuten. *Ztschr. f. Klin. Med.*, 113:379, 1930.
11. Keefer, C. S., and Bloomfield, A. L.: The Significance of Gastric Anacidity. *Bull. Johns Hopkins Hosp.*, 39:304, 1926.
12. Davies, D. T., and James, T. G. I.: Achlorhydria and Anemia in Advancing Years. *Lancet*, 2:899, 1930.
- An Investigation into the Gastric Secretion of a Hundred Normal Persons Over the Age of Sixty. *Quarterly Jour. of Med.*, 24:1, 1930-31.
13. Bloomfield, A. L., and Keefer, C. S.: Gastric Acidity: Relation to Various Factors Such as Age and Physical Fitness. *Jour. of Clin. Invest.*, 5:285, 1928.
14. Pollard, W. S., and Bloomfield, A. L.: Gastric Anacidity. *Arch. Int. Med.*, 48:413, 1931.
15. Lerman, J.; Pierce, F. D., and Brogan, A. J.: Gastric Acidity in Normal Individuals. *Jour. Clin. Invest.*, 11:155, 1932.
16. Vanzant, F. R.; Alvarez, W. C.; Eusterman, G. B.; Duan, H. L., and Berkson, J.: The Normal Range of Gastric Acidity from Youth to Old Age. *Arch. Int. Med.*, 49:345, 1932.
17. Hartfall: Achlorhydria. *Guys Hospital Reports, London*, 82:13, 1932.
18. Arnold, L.: The Bacterin Flora Within the Stomach and Small Intestine. *Amer. Jour. Med. Sci.*, 186:471, 1933.
19. Arnold, L., and Hood, M.: A Study of the Relationship Between Acid-Base Equilibrium and Bacterial Flora of the Stomach. *J. A. M. A.*, 101:2145, 1933.
20. Soper, H. W.: Milk. *Amer. Jour. of Digest. Dis. and Nutrit.*, 2:113, 1935.
21. Arnold, L., and Stewart, C.: Recent Development in the Study of Oral Bacterial Flora. *Am. Jour. of Digest. Dis. and Nutrit.*, (in press).
22. Hanszen, A.: The Bactericidal Power of the Stomach and Some Factors Which Influence It. *Am. Jour. of Digest. Dis. and Nutrit.*, 1:725, 1934.
23. Gulbrandsen, L., and Arnold, L.: A Preliminary Study of Gains in Weight, Between Meal Feeding and Gastric Response Using a Chocolate Flavored Milk Product. (in print).

## ABSTRACTS

DR. GRAUMANN.

*The After Treatment of Ulcer Patients Following Resection of the Stomach.* *Munch. Med. Wocheu.*, 82, No. 4, Jan., 1935.

Many patients display identical complaints following resections of the stomach as they had before operation. Evidently this is mostly due to the persistency of gastritis preceding the operative procedures.

Ulcer complaints are due partly often to an accompanying gastritis and as such can not be obviated suddenly by operative measures. In fact such pathology becomes more accentuated in view of the mechanical handling of the stomach wall itself. An increase of hyperacidity in such cases is also the consequence of increased irritation of the mucosa.

The feeling of fullness owes its presence to a decreased capacity of the stomach. Post-operative vomiting is often the consequence of mechanic disturbances although incarceration of loops of the mesocolon must also be thought of. Occasionally a self torsion of the afferent loop or a strangulation is to be looked for. A submucosal swelling with a tendency to reduce capacity of the loops involved in the anastomosis may also be responsible for regurgitation of food.

Therapeutically the administration of "Gastro-Sil" seems to help greatly. The drug is a calcium silicat jel which forming a jelly-like mass protects the mucosa from undue irritation. The neutralization of the acids lasts longer and there are no astringent irritations encountered with this drug as seen with other alkalies. It seems that the calcium content embodied in this drug also reacts favorably in that it reduces inflammatory tendencies in the tissues having a haemostyptic action also. A decrease of chlorides is greatly diminished with this drug, another reason why it can be given without the fear of producing uremic symptoms.

M. E. Gabor, Milwaukee.

FOGELSON, SAMUEL J.

*Gastric Mucin Treatment of Peptic Ulcer; a Report Based on Questionnaires.* *Arch. Int. Med.*, Vol. 55, No. 1, pp. 7-16, January, 1935.

For five or six years past Fogelson has been trying to determine the efficacy of gastric mucin in the treatment of

gastro-duodenal ulceration; and this paper reports the results in approximately 555 cases observed during the past three years. These patients were followed not only by Fogelson himself but also by a Gastric Mucin Committee appointed by the Northwestern University Medical School of Chicago and by all other physicians sufficiently interested to co-operate by reporting, on a questionnaire furnished them, the data at outset and during the progress of treatment.

Detailed statements were given by these different men, to whom mucin was supplied for use in treatment, after the material had been accepted by the Committee as suitable and proper in every respect. These statements covered the history of the case, the X-ray findings, recurrences, incidence of hemorrhage and the effects of former treatment, including surgical procedures; as well as the progress of the case and the effects of treatment by mucin. The average dose was 80 to 100 grams of dry mucin powder, suspended in a mixture of milk and cream, at frequent regular intervals, as often as every hour in acute cases. The diet was limited to the bland substances usually prescribed in ulcer. The treatment was continued for at least six months, the dosage, however, being reduced during the late stages.

The results were highly satisfactory, considering the fact that only cases were selected for treatment that were previously considered intractable, because they failed to respond to ordinary methods. Of 555 who took mucin from six months to three years, 348 were rendered free from symptoms, 114 were partially improved and 93 failed to secure relief. Of the latter, however, only 32 were counted true failures, because the other 61 for various reasons would not continue the use of mucin for an adequate period. Recurrence of symptoms while still receiving mucin was noted in six persons, acute massive hemorrhage in four and perforation in one. In 56 patients with a recurrence of symptoms after gastro-enterostomy, suggesting a new ulcer at the gastro-enterostomy stoma, complete control of all the subjective symptoms was obtained by the use of mucin in 36, partial relief in 16 and no relief in 4.

The one important question not yet answered is the permanence of the results obtained; and this can not be answered until more time has elapsed.

Wm. Fitch Chaney, San Francisco.

## SECTION V—*Therapeutics*

### The Treatment of Food Allergy and Indigestion of Pancreatic Origin with Pancreatic Enzymes

*By*

ANTON W. OELGOETZ, M.D.

PAUL A. OELGOETZ, B. A. (Chem)

*and*

JUANITA WITTEKIND, R.N.

COLUMBUS, OHIO

**I**N a previous communication (1) we reported the results of an investigation concerning the rôle of the pancreatic enzymes in the etiology of food allergy and indigestion of pancreatic origin. The present paper will concern itself with the use of the pancreatic enzymes in the treatment of these conditions.

It was indicated in our previous studies that, contrary to present teaching, the stomach and duodenum are not the essential organs of digestion. Food is not completely digested in the stomach and the duodenum. The function of the stomach is to act as a receiving and mixing hopper, where, under the influence of acid-pepsin the food mass is reduced to a homogeneous, semi-liquid state.

Probably a small amount of absorption takes place directly from the stomach, but most of the stomach contents pass into the duodenum where they combine with the pancreatic enzymes.

The function of the duodenum and jejunum is absorption of the food mass combined with pancreatic enzymes, and of free pancreatic enzymes. During the process of absorption in the duodenum some of the food is split to the various derived proteins and amino-acids, but the bulk of the duodenal contents, changed in varying degrees all the way from alkali-metaproteins to amino-acids, but principally as alkali-metaproteins, pass into the blood stream. Hydrolysis or digestion in the duodenum may be incidental, much of the essential process of digestion taking place in the blood stream.

We have pointed out that, in order to exhibit optimal enzyme activity, enzymes must function under certain standard conditions. The concentration of enzymes must be constant; the concentration must bear a definite relationship to the quantity of substrate (food); the pH of the medium must be approximately 7.6; the temperature must be 98.6. None of these necessary conditions always is present in the stomach of duodenum.

In the blood stream however, normally conditions are perfect for optimal enzyme activity. Here the pH is always 7.6; the temperature always 98.6; the concentration of enzymes always constant, namely 0.2 as

determined by the test suggested by us; and the substrate (serum proteins and fats) always constant, except for short periods immediately following meals. Here we have conditions entirely perfect for optimal enzyme action, with none of the disturbing factors, such as intake of water (which dilutes the enzymes and substrate), the taking of irritating drugs and other substances, which inhibit the action of enzymes.

We have shown that normal serum always contains the three pancreatic enzymes, amylase, protease and lipase, and that these enzymes would seem always to be present in a definite and constant concentration which is uninfluenced by intake of food, exercise or sleep. In short, the blood which is continually "digesting itself" is an essential organ of digestion.

Because the main degree of final digestion does not take place in the stomach and duodenum (except incidentally) we believe that it is irrational to test for and attempt diagnostic appraisal as to capacity of these enzymes in the secretions of the duodenum. The pancreatic enzymes pass into the duodenum, where, when food is present, they combine with the food and thence pass into the blood stream. If no food is present, we believe that we have shown that the free enzymes pass into the blood stream where they circulate, (as free enzymes) acting as buffers, combining with and splitting any food derivatives which have gained entrance to the blood stream uncombined with enzymes.

Thus, in our opinion, based upon extensive studies, the duodenal secretions at any given time contain but a small fraction of the total daily pancreatic secretion, (external secretion). The duodenum at any given time contains only those enzymes which are in process of being absorbed, which are "en route" through the duodenum, on their way to the blood stream. Testing the duodenal secretions for enzyme concentration therefore is at best but a rough qualitative test. The question is not whether or not enzymes are present, but in what concentration. The only place in which the actual concentration of enzymes can be determined is in the blood stream. It is in the blood stream where the enzymes find their field for action, where, in health,



they are always found in a definite, constant concentration.

The serum enzymes can be qualitatively determined by the usual tests, but this requires that three tests be made; necessitates too large a quantity of serum; and is too time-consuming and too technical to be used in daily practice. Consequently, we have devised a more practical test which can be more quickly and easily done. The test is based upon the fact first noted by us, that serum assumes an increasing iodine value as digestion advances. Our test, described in detail elsewhere, gives a moving picture, a cross section of the continuing hydrolysis as it takes place in the blood stream.

As has been noted, the serum enzymes are always present in the serum in a definite and constant concentration. Likewise, if the tissues and organs of rabbits are ground with quartz sand and extracted with distilled water, it will be found that every tissue and organ in the body, with the exception of the heart and brain, contains the serum enzymes in a concentration exactly 100 times that of serum. It therefore appears that the cells of the body live in a solution of enzymes, making it impossible for any substance to reach the cells without first having run the enzyme gauntlet, which splits the substance to a harmonious form which can be used as food by the individual cells.

On the other hand, if, as a result of pancreatic hypofunction, the concentration of serum enzymes falls below normal, so there are not sufficient enzymes to split all of the food taken, whole, unracemized proteins reach the cells and exert their own physiological action which is essentially that of "irritation," using the word in a broad sense. In our opinion, it is this irritation caused by whole, unsplit, "disharmonious" proteins which causes the symptom-complex which has been called "food allergy." When truly foreign substances such as bacteria or bacterial products which cannot be split by the serum enzymes, gain entrance to the blood and thence to the cells, there follows the other type of allergy which results in the formation of specific anti-substances or antibodies.

If the serum from a patient is found by our test to show an iodine index of 0.2, that patient exhibits the enzymes in normal concentration, indicating that the pancreas is secreting its enzymes (the external secretion) in normal quantity. Such individual will not suffer from allergy because sufficient enzymes are present to completely split and reduce to a "non-irritative" form all of the food which is taken.

If however, the patient shows an iodine index of minus 4, for example, the serum enzymes are not present in normal concentration, evidently because the pancreas is not secreting its normal, daily complement of enzymes. In such instance, the blood stream contains varying quantities of whole, unracemized proteins which exert their irritative action on the cells and thus produce the allergic state.

Thus it will be seen that according to our conception, allergy to foods is caused by an excess of food—not an excess from the viewpoint of bodily requirements (indeed, many of these patients are underweight) but an excess with reference to the ability of the pancreas to secrete the necessary quantity of enzymes for complete digestion. In short, the food intake exceeds the pancreatic threshold. This excess may be in the form of one particular food, beef, for example, but more often it is the combined excessive

intake of *all* foods which causes the anomaly. This is the reason why one observes such contradictory results from the skin scratch tests; why an allergic patient will react positively to beef at one sitting and a week later, though still allergic, will react negatively to beef, and positively to some other food which was negative in the first instance. It is the *excessive total food intake* which surpasses the pancreatic threshold, which is the cause of food allergy.

Thus, if the iodine number of serum gives a minus index, the patient is allergic, is taking too much food, more food than can be split by the available enzymes. However, in many instances this pancreatic hypofunction is merely latent, that is, the pancreas secretes sufficient enzymes for all of the usual food requirements, and a shortage only occurs from an occasional excessive food intake. For example, consider a certain patient, a sales' manager. Ordinarily, when on his regular ration, this man is free from digestive or allergic disturbances. But once each month he is required to preside at a sales' meeting, which is always concluded with a big dinner. At such times he overeats (and drinks) and temporarily, in our conception, exceeds his pancreatic threshold. The next day invariably he turns up with a marked case of angio-neurotic oedema. Our interpretation is that his pancreas is equal to all normal food-intake demands when on customary rations but proves quantitatively inefficient when his food intake temporarily becomes excessive.

When this type of case is tested during an attack, he will show a minus index. But if he is tested in the interim between attacks, when on his regular ration, he will show a normal index. In order to uncover this type of case, usually seen after the attack when the serum again is normal, we have devised an *overfeeding test*. The serum is tested the first day in order to determine the normal index. The patient is then directed to overeat—take an excessive quantity of food. We make no effort to have him take a definitely increased caloric ration, but simply direct him to double his customary ration. If he is in the habit of eating one egg for breakfast, we have him take two; if he usually eats but one helping of meat, we direct him to double the portion. In this manner we have him take a definitely increased quantity of all food substances.

He returns the next day when his serum again is tested. If the pancreatic index is normal, shows the normal concentration of serum enzymes, we conclude that his pancreas is exhibiting a normal threshold and is able to digest a normal quantity of food. Such patient will never suffer from indigestion (secondary to pancreatic hypofunction) or food allergy. However, if on the second day, the serum enzymes are found in a definitely reduced concentration, it indicates that the pancreas was unequal to the extra demand; in short, the patient suffers from latent pancreatic hypofunction. It is these latent cases of hypofunction which would seem frequently to account for acute allergic states, such as urticaria, angio-neurotic oedema, etc., which only result occasionally, usually following dietary indiscretions.

The word "indigestion" has been used in this paper. This word generally is rather loosely used and usually indicates any disturbance of digestion which might result from a host of factors which interfere with the digestive processes. For instance, indigestion frequently accompanies gall bladder disease, ulcer of the

stomach, etc. But the indigestion referred to in this paper is that form which results from a shortage in the serum concentration of enzymes or pancreatic hypofunction. In many cases a latent hypofunction is of mild degree, not sufficient to give an allergic response. Such patients simply complain of "indigestion" which however, is a true indigestion resulting from a shortage of pancreatic enzymes. In cases suffering from a greater degree of pancreatic hypofunction, many of the symptoms complained of as "indigestion" are true allergic manifestations which promptly clear up when the underlying pancreatic hypofunction is corrected.

Hypofunction of the pancreas results from many causes. Thus we find hypofunction secondary to gall bladder disease, with secondary infection of the biliary and pancreatic ducts; following such general infections as syphilis; accompanying congestive states, such as a defective myocardium. In many instances, however, the hypofunction is primary.

Frequently, in borderline cases the pancreas is equal to everyday demands and only shows evidence of hypofunction when under unusual stress, as after a food debauch. It follows therefore that each case should be given a thorough physical examination so as to uncover and correct any other associated trouble, in addition to correcting the pancreatic hypofunction. In many cases, hypofunction and the resulting allergic state is the cause for the continuance of a primary trouble. For example, only recently we saw a woman who was suffering from oedema of the ankles, secondary to a defective myocardium. She also experienced a distressing asthma, in our opinion of pancreatic origin. Because the asthma threw an additional burden on the crippled heart, it increased her cardiac difficulty. When the causative pancreatic hypofunction had been corrected her heart carried on very decently.

### TREATMENT

In cases of *acute allergy following occasional excessive food intake*, the only treatment necessary is temporarily to reduce the total food intake, and perhaps give a saline purge to remove the excess unsplit food from the bowel. In the course of a day or two the pancreas "catches up" and the trouble subsides. In chronic cases, however, in which the serum enzymes can be shown objectively to be continually below normal, and in which correction of any primary trouble does not restore the pancreas to normal function, it becomes necessary to help the overworked pancreas by the exhibition of pancreatic substance—i.e. "substitution therapy" as is to commonly exhibited when the thyroid gland proves unequal to physiologic demands. When given in the usual doses, pancreatic substance has not been found effective in restoring the serum concentration of serum enzymes. This is due in part to the fact that much of the pancreatic substance on the market is physiologically inert. In the test tube, when set up under conditions making for optimal activity, the quantity of pancreatic substance usually given is sufficient to digest all of the food usually taken. The reason why pancreatic substance when given by mouth is not so effective as in the test tube is because a large part of the dose taken is destroyed by the pepsin in the stomach, and only a fraction of the dose reaches the duodenum in an active state. It has been believed that because pancreatic substance is a protein substance, it is digested by the pepsin. This

however, is not correct, because when added to pepsin, pancreatic substance, so far as its physiologic action is concerned, *instantly* is destroyed before it could possibly be digested. It has been believed that the acid of the stomach destroys the action of pancreatic substance. This view likewise is incorrect. Many times we have permitted pancreatic substance to remain in solutions of hydrochloric acid for many hours without destroying it. It is true that pancreatic substance does not exhibit its optimal activity in an acid medium, but acids do not completely stop its action; nor do they destroy the enzyme; they do however, slow up its action. When the necessary conditions of alkalinity for optimal activity are restored, pancreatic substance again becomes normally effective. What then is the answer? The following experiment will make clear the problem.

Place a quantity of egg albumin in a "U" tube and coagulate. Now fill both arms of the tube with pepsin solution. Connect the arms of the tube with an electrical current. It will be found that in the positive arm the pepsin digests the albumin, the pepsin passing deeper and deeper into the albumin. However, in the negative arm it will be found that digestion does not take place. It will also be noted that the pepsin travels toward the negative pole. This indicates that pepsin in colloidal dispersion carries a positive electrical charge. If pancreatic substance is substituted for the pepsin in the same experiment it will travel toward the positive pole, indicating that pancreatic substance in colloidal dispersion carries a negative electrical charge. If a solution of pancreatic substance is added to a solution of pepsin, the positively charged pepsin particles are electrically discharged by the negatively charged pancreatic particles, and therefore, both solutions are inert, that is, have lost their enzymic activity. Thus the reason why pancreatic substance is partially destroyed in the stomach is because the electrically positive pepsin discharges the electrically negative pancreatic substance. But in order to be completely discharged and rendered inactive, the pancreatic particles must meet an equal number of pepsin particles, just as a given quantity of tenth-normal sodium hydroxide requires an equal quantity of tenth-normal hydrochloric acid for complete neutralization.

Just as a weaker solution of hydrochloric acid will not completely neutralize an equal quantity of tenth-normal sodium hydroxide, so an excess of pancreatic substance will not be completely destroyed by pepsin. The following experiment will make this point clear.

Set up a series of tubes, each containing  $\frac{1}{2}$  c.c. of a colloidal solution of pancreatic substance. To the same tubes add respectively, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 c.c. of a colloidal solution of pepsin. Shake and incubate. Meanwhile, set up another series of tubes, each tube containing 2 c.c. of soluble starch solution. Now, to the starch tubes add  $\frac{1}{2}$  c.c. of the successive pepsin-pancreatic substance mixtures. Thus we have a series of tubes, each tube containing 2 c.c. of soluble starch solution, plus  $\frac{1}{2}$  c.c. of pepsin-pancreatic solution, the quantity of pepsin varying in each tube.

When the tubes have incubated for several hours, they are titrated with Fehling's solution to determine the quantity of sugar. It will be found that the quantity of sugar is greatest in that tube containing the smallest quantity of pepsin, and least in that tube containing the largest quantity of pepsin, thus indicating that a given quantity and strength solution of pepsin is only completely discharged by the same quantity and strength solution of pancreatic substance; and that if there is an excess of pancreatic substance, the excess remains undischarged. Consequently, it follows that

if sufficient pancreatic substance is given by mouth—sufficient to discharge the pepsin present in the stomach plus an excess—the excess passes uninjured and active into the duodenum.

Clinically, we have found this to be the case. If pancreatic substance is given in large enough dosage—from 75 to 90 grains daily—sufficient will reach the duodenum in an active state to effect the serum level of enzymes. However, practically, this is a very wasteful and unscientific manner in which to give pancreatic substance, as only a small part of the dose given reaches the blood in an active state. Then, too, most patients bitterly complain when required to take such large doses, as pancreatin is an exceedingly nauseating substance which often produces gastric irritation. When taken in the dry form, whether in the form of the powder suspended in water, the pill or capsule, the dry substance must first be put into solution before it can be absorbed. This requires time and it is during this time that it comes under the prolonged action of pepsin. When given in capsules the material is more pleasant to take; however, the regular gelatine capsules dissolve at once in the stomach, thus liberating the pancreatic substance which is discharged by the pepsin as it passes into solution. There is no essential difference between taking pancreatic substance in the form of the powder suspended in water, or taking it in the regular gelatine capsule.

Gelatine capsules can be hardened by exposing them to formaldehyde gas (glutol capsules). However, the time required for a capsule to pass through the stomach varies so greatly in different individuals that it is impossible to harden a capsule to the "just right" degree which will carry the material through the stomach in every instance, and then promptly break up in the upper bowel. It has been our experience that capsules either are hardened too little, in which case they break up in the stomach, or they are hardened too much, when they pass intact through the entire gastro-intestinal tract. After many attempts we have found it impossible to process a capsule to the correct degree of hardness so that it will always break up in the upper bowel.

Enteric coated pills likewise have been found unsatisfactory. It is impossible to apply an enteric coating which will protect the pill contents against the stomach secretions for varying periods—from 15 minutes to 4 hours—and then promptly break up in the upper bowel. We have many times recovered enteric coated pills from the feces. Because pills are pressed tightly in the process of manufacture, they break up very slowly, many only partially or not at all. We have recovered pills from the feces even when the enteric coating had first been removed. Another disadvantage is that the pressure used in making the pill seems to have an inactivating effect upon the enzymes.

Clinically, we have found that the pancreatic enzymes are best given in the form of a 50 per cent glycerin extract of the whole pancreas. The enzymes are soluble in glycerin and Haidenhain has found that a glycerin extract will remain active for 20 years (3). Because the pancreatic enzymes find their field of action in the blood stream and not in the bowel, it is not necessary that they pass into the duodenum. When

administered in glycerin, all three pancreatic enzymes (because they are already in solution in glycerin, which is itself a product of digestion and is therefore not attacked by the gastric juice) are immediately absorbed into the blood stream. After many trials with all other forms, we are convinced that a 50 per cent glycerin extract of the whole, fresh pancreas is therapeutically the most efficient, and scientifically the *only exact* form in which to administer the pancreatic enzymes. A quantity of glycerin extract equal to 5 grains of an active dry powder, after each meal, preferably given in a gelatine globule, has been found to be clinically effective in cases exhibiting the highest degree of hypofunction (minus 4). That pancreatic substance is effective, even when given by pill, is evidenced by the report of Sansum who contacted 280 patients who came under the classification of "indigestion" (of pancreatic origin) underweight and allergy (2). The cases of allergy comprised urticaria, eczema, angio-neuritic oedema, allergic indigestion, allergic rhinitis, allergic migraine, joint allergy, hay fever, and bronchial asthma. Under treatment with pancreatic substance 129 of 152 instances of allergy or 85% improved; 23 or 15% did not improve; and 9 did not follow the plan outlined. Of the 143 who followed the plan 129 or 90% improved, while 14 or 10% did not improve.

In our own series of 100 cases we encountered approximately similar results. The problem of truly interpreting the results of treatment is made difficult by the fact that many cases of allergy are complicated by the presence of secondary diseases. Asthma, for example, is very often accompanied by chronic bronchitis and varying degrees of emphysema; and these complicating anomalies must be taken into consideration in any evaluation of results of treatment. It is our distinct impression that results are always excellent if too much permanent damage has not already taken place when treatment is commenced.

The serum level of enzymes cannot be made to go above a concentration of 0.2 by the test which we have suggested. When given in excessive dosage, pancreatic substance is completely absorbed and stored in the active state, principally in the spleen, from which it is gradually liberated in such concentration as to maintain the normal serum level. Even when 200 grains are taken at one time, the substance is completely absorbed, none of it appearing in the urine and feces. The absorption and fate of pancreatic substance when taken by mouth will be fully discussed in a later paper. Apparently, the enzymes are not toxic when given in large doses; nor do they injure the kidneys, as we have never encountered a case in which the urine showed signs of irritation.

### CONCLUSIONS

1. "Indigestion," secondary to pancreatic hypofunction is a fairly common cause of digestive disturbances.

2. Food allergy may be caused by a decrease in the concentration of serum enzymes, which permits whole, unracemized proteins to reach the body cells, where, because they cannot be used as food, they exert their own physiological action which is essentially that of irritation.

3. The administration of pancreatic substance in the form of a glycerin extract of the whole gland by

mouth, is therapeutically justified and clinically effective.

4. Patients who are allergic to foodstuffs and in whom too much permanent damage has not resulted when treatment is commenced, usually improve promptly when given an active glycerin extract of pancreatic substance.

5. Allergy to foodstuffs can be diagnosed and treatment controlled by a simple test which we have described elsewhere.

This work was encouraged by a grant from Fairchild Bros. and Foster of New York, who also made available for clinical use generous quantities of Holadin, a highly active extract of whole pancreas.

#### REFERENCES

1. Oelgoetz, A. W.; Oelgoetz, P. A., and Wittekind, J.: Studies in Food Allergy: a Preliminary Report. *Am. Jour. Digest. Dis. and Nutrit.*, p. 730, Vol. 1, No. 10, Dec., 1934.
2. Sansum, W. D.: The Treatment of Indigestion, Underweight and

- Allergy With the Old and New Forms of Digestive Agents. *Southwestern Medicine*, Nov., 1932.
3. Imldenhaln, R.: Beitrage Zur Kenntnis Des Pankreas, *Pflüger's Archiv.*, p. 557, 1875.

## Histidine in the Treatment of Peptic Ulcer: a Preliminary Report\*

By

JOHN T. EADS, M.D.

PHILADELPHIA, PENNSYLVANIA

THE injection treatment of peptic ulcer has been popular for several years, perhaps in an effort to find some shortcut to a permanent cure thereby avoiding the drawn out dietary and alkaline regime so often the despair of the patient and physician alike. While both orthodox medical and surgical treatment at times fail to achieve the desired result, the final analysis of cures effected compares favorably thus far with the newer modes of therapy.

A number of methods of the injection treatment have been used. To mention a few, C. R. Jones has used insulin. Glaessner uses injections of pepsin. Cunha reports favorable results with "synodal." Van Kleec and others have used sodium citrate and sodium chloride intravenously. Favorable results have been reported by practically all of the various methods in use today. Only a few, however, have had sufficiently long periods of observation for any accurate estimation of their real value.

Quite a few foreign authors have used preparations of amino acids in the treatment of peptic ulcers. Most of this work has followed the experimentation of A. G. Weiss and E. Aron of Strassburg. These authors repeated the experiments of F. C. Mann and produced jejunal ulcers in dogs by shunting the gastric contents directly from the stomach into the jejunum. They, as did Mann and others, found that exposure of these experimentally produced ulcers to normal duodenal contents resulted in their rather prompt healing. When the duodenal contents were withdrawn and gastric juice again permitted to course over the area the ulcers were re-activated. Weiss and Aron experimented with various amino acid preparations and found that certain of these were effective in healing these experimentally produced ulcers. They concluded that a preparation of histidine was the most effective in this respect.

Histidine is an amino acid produced by protein digestion and is supposedly essential for cell life. The actual mechanism of the action of this amino acid in the healing of these ulcers is by no means clear. There

may be some explanation in its essential rôle as a factor necessary to cell integrity and repair. It also may be a factor in causing a secretion rich in the protective and acid combining mucin.

Most of the clinical use of this treatment of peptic ulcers has been reported by foreign investigators. Weiss and Aron, Blum, J. Lenormand, George Hessel, L. Bogendorfer and Ernest Bulmer have all reported its use in small series of peptic ulcers in humans. The reports are for the most part concerned with immediate results, the follow-up on many of the cases being insufficient.

However, for the most part these authors report favorably on this method of treatment. It appears that immediate clinical improvement resulted in the majority of their cases with X-ray changes indicating healing and in many instances complete disappearance of the characteristic ulcer deformity. Reduction in the gastric acidity was also reported by some and in no instance were any unfavorable reactions noted. Gastric ulcers responded better than duodenal as a rule.

In this country, at present, there have been very few reports on the usage of this form of treatment. Vilini and McLaughlin report favorably on its use both as to clinical results and in the reduction of the acidity of the gastric secretion.

The method of treatment was practically the same with each author—a 4% solution of histidine hydrochloride was used. It was given in daily injections of 5 c.c. either subcutaneously or intramuscularly, the intramuscular route being preferred. From the experimental evidence the best results were obtained when the average course of treatment extended over a 21 to 24 day period. Bulmer and Bogendorfer report the largest series of cases treated, the intramuscular route being used and a daily dosage of 5 c.c. of the histidine solution given for periods of approximately 24 days. No unfavorable complications were observed. Good results were reported. Bulmer reported 58% symptomatic cures with disappearance of abnormal X-ray findings, 19% clinical improvements with no radiological changes and 23% failures in his series of 52 cases. A large number of these were gastric ulcers.

\*From the Medical Department, Jefferson Hospital, Philadelphia. The preparation of histidine solution used in this series of treatments is Larostidin supplied by Hoffmann-LaRoche, Inc., Nutley, N. J. Submitted August 1, 1935.

Case 1. A typical ulcer history for one year. The film at the left shows a gastric ulcer of the lesser curvature. The one at the right shows its disappearance after 24 injections of histidine. Relief obtained after the sixth injection—no diet or medication. No recurrence after six months.

### METHOD OF STUDY

Since October, 1934, we have treated 35 cases of peptic ulcer with histidine injections. Practically all cases have received a minimum dosage of 24 daily intramuscular injections of a 4% solution of histidine hydrochloride. Several cases have received as many as 36 injections. Only those cases definitely diagnosed peptic ulcer both clinically and from an X-ray point of view were selected. For purposes of record a careful history in each case was taken. The patient's weight, complete blood count, gastric analysis, pulse, blood pressure and roentgen findings were recorded before treatment was instituted. In addition, each patient was given an intradermal test, using 1/20 c.e. of the histidine solution, before the proposed course of injections were started. At various times during the treatment the gastric acidity curve was determined. No special diet or medication was followed except in some instances, where hospitalized, patients were given occasional doses of alkalis or told to omit such articles from their diets known to cause them trouble. None of the patients was confined to bed and the majority was permitted to continue usual occupations.

The number of cases observed during this particular study is not a large one, but it compares favorably with the series reported by other authors. Bulmer reports on 52 cases, Bogendorfer on 30 cases, Hessel on 22 cases, Weiss, Aron and Lenormand on several smaller series, Volini and McLaughlin on a series of 21 patients.

The follow-up of this series of 35 cases consists of a six-month observation period. Naturally, this is too short a period of observation to determine the permanency of results, but for the most part the same can be said of all the other reported series of cases similarly treated.

This report is, then, in the nature of a preliminary one, and the work is to continue with a subsequent report on a larger series of cases as to more or less immediate results together with a reasonable period of follow-up observation.

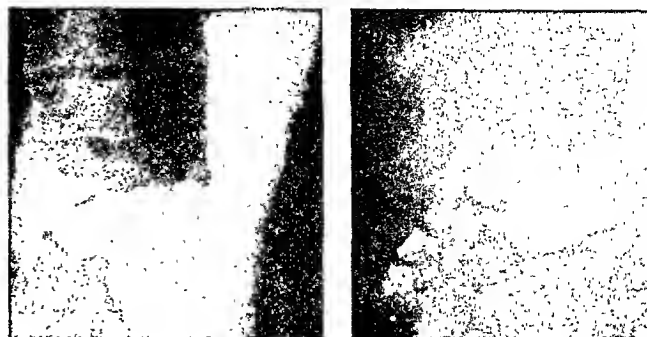
### DESCRIPTION OF CASES

1. In this series there were 35 cases of peptic ulcer, of which 30 were duodenal and 5 gastric in type, the percentage of gastric ulcers being generally less than in those series of cases reported abroad. There were 32 males and 3 females in this series. The oldest patient was 59 years of age, the youngest 23 and the average age 41 years.

2. The average duration of symptoms for the entire group was  $7\frac{1}{2}$  years, the longest history being 12 years and the shortest 2 months.

3. 24 of these patients had been on some other form of ulcer treatment prior to the histidine treatment. 11 had received no treatment. The results in those patients already treated had been generally unfavorable.

4. 26 of this series of 35 cases presented a gastric hyperacidity prior to the institution of the treatment. 7 gave practically normal acid figures and in 2 cases there were low acid figures.



Case 1

5. There were 8 cases who presented some degree of obstruction with a varying degree of gastric retention.

6. There were 3 ulcers in which some gross hemorrhage had taken place.

7. 2 cases had been subjected to previous operative procedures (gastro-enterostomies), one with a reactivation of the duodenal ulcer, the other diagnosed as a marginal ulcer.

8. Pain or discomfort with or without direct relationship to meals was the most common complaint in each case.

### ANALYSIS OF IMMEDIATE RESULTS

1. There were no noticeable local or systemic reactions.

2. There was no appreciable change in the blood pressure or pulse rate determination after each injection.

3. The intradermal test was positive in 7 cases out of 28 in which it was used. This may be of some significance in that it was positive in those cases showing the best results.

4. The blood counts were generally unaffected by the treatments.

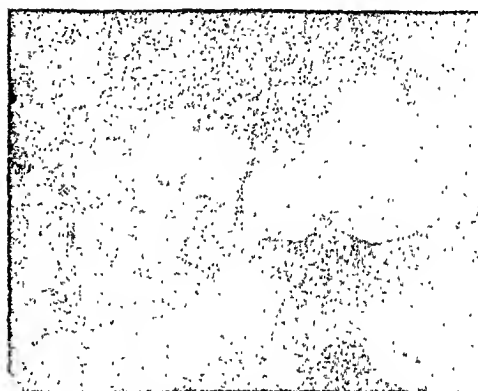
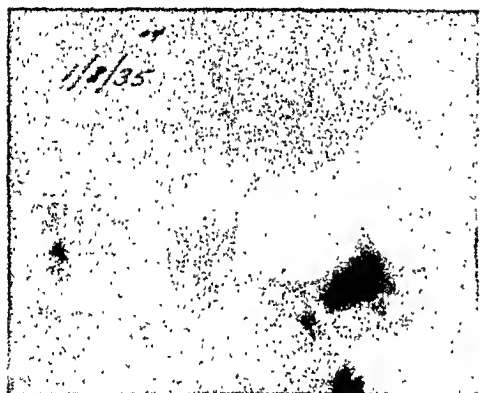
5. 16 patients exhibited a gain in weight during the course of treatment. 13 cases remained fairly stationary and 6 showed a loss in weight. The greatest gain was 21 pounds, the lowest gain 2 pounds and the average gain in the 15 cases was  $5\frac{1}{2}$  pounds. A gain in weight often began early in the treatment.

6. In this series of cases the gastric acid curve remained generally unaffected except in 5 cases. In these 5 cases in which a rather marked hyperacidity was present some reduction was noted, but not to normal figures. A total of 118 gastric analyses were done on this series of cases. An ordinary tea and toast meal was used with the location of the tube always the same and with the test meal always at the same time of day. These findings with regard to lack of acid reduction are at variance with some of those reported by other investigators, notably Volini and McLaughlin.

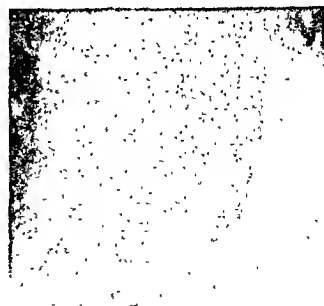
7. In the majority of cases in which improvement was noted it occurred relatively early in the course of treatment, usually after the fifth injection. The improvement symptomatically consisted in relief of discomfort, a gain in appetite and weight and a tolerance for a more normal dietary.

8. No improvement was noted in the patients presenting signs of an obstructive lesion causing gastric retention, even after a full course of injections were given and in some instances after 36 or more injections.



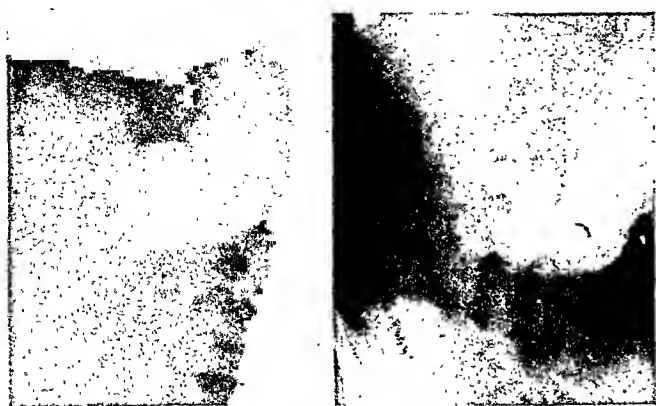


Case 2. A 10 year history of ulcer, repeatedly studied over that period and so diagnosed. Had been on medical treatment with very little benefit. The films at the top illustrate the deformed duodenal cap before the histidine was given. Those below show the change in appearance after treatment. Symptomatic relief obtained after 5 injections and continued. X-ray evidence of improvement after 10 injections.



Case 3. A two year history of ulcer with hemorrhage at times. From left to right films show an ulcer of the lesser curvature. In the last film the ulcer has practically disappeared after 15 injections of histidine. Patient operated because of hemorrhage. Scar found at site of previous ulcer. No diet or medication. No recurrence after 4 months.





Case 4

9. The X-ray findings were variable. There was a disappearance of radiological evidence of ulcer in 6 cases. In 8 other cases there was definite improvement in the X-ray findings. In the remaining patients there was little or no change noted, even several months after the series was completed. In the accompanying illustration of the X-ray films in 6 cases, the change in the characteristic deformity readily can be recognized. Disappearance of radiological signs was rapid in several cases. The illustrations show the radiological findings before and after the course of treatment.

10. There was distinct improvement both clinically and roentgenologically in both the patients upon whom operations previously had been performed.

#### CLASSIFICATION OF IMMEDIATE RESULTS

6 cases or 17.1% showed clinical and X-ray evidence of immediate healing.

8 cases or 22.8% showed evidence of clinical and X-ray improvement.

9 cases or 25.7% showed evidence of amelioration of their symptoms but no X-ray change.

12 cases or 34.3% were unimproved at the completion of the course of treatment.

These immediate results are not as favorable as other authors have reported. Most of the other investigators have had a larger percentage of gastric ulcers; these appear to respond better than duodenal. The average duration of symptoms in this series is longer than it is in the histories of other cases reported. These factors may to some extent influence the picture.

#### DISCUSSION

Thirty-five cases of peptic ulcer were treated with intramuscular injections of a 4% solution of histidine hydrochloride, averaging a series of 24 injections with no local or systemic reaction.

Six of these cases (17.1%) showed immediate clinical and X-ray evidence of cures. Of these 6 cases, 3 were gastric ulcers and 3 were duodenal. The average history of symptoms in these 6 cases was 2½ years—much less than the average of the entire group. Symptomatic relief of distressing complaints was early—usually after the first three or four injections. The

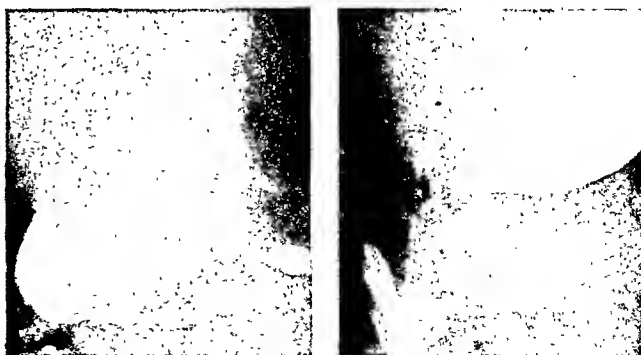
Case 4. A typical one year history of duodenal ulcer. Film at the left shows the deformity of the duodenum. At the right can be seen the duodenum filled normally after 24 injections of histidine—no diet or medication. Relief of symptoms after 4 injections. No return of symptoms after 6 months.

gain in weight in these cases was the most marked. None of these patients was restricted as to diet or placed on medication. Four of these 6 cases demonstrated a positive intradermal reaction. None of them, after a period of observation of 6 months or more, has shown any recurrence. Five of these cases showed some decline in the acid curve but not to normal figures. All of these cases presented a disappearance of the characteristic deformities seen at X-ray.

Eight cases (22.8%) presented definite clinical and X-ray improvement, not so rapidly as the first group, but still it was definite. There were 6 duodenal ulcers and 2 gastric ulcers in this group. A gain in weight was shown by 6 of these cases, 2 showed no gain. Three presented positive intradermal reactions. Five began to show improvement after the tenth injection, 2 after the fifteenth and the remaining one after the twenty-third injection. Five of these cases were on no dietary restrictions, 3 were advised regarding elimination of tobacco, coffee, alcohol, et cetera and one had alkalies at times, but not regularly. The average history of duration of symptoms in this group was 4½ years.

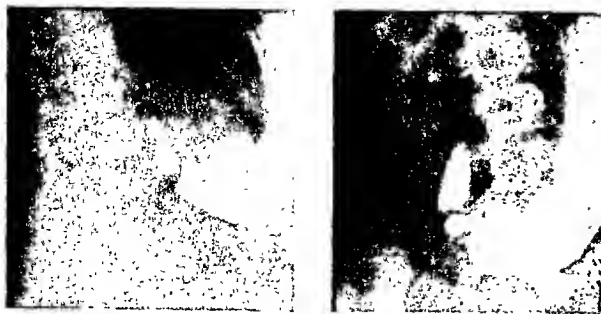
Nine cases (25.7%) showed some clinical improvement, but no X-ray change at all. The symptomatic improvement was much slower than it was in the other two groups and not until eighteen or more injections had been given was any improvement noted. These were all duodenal ulcers with an average history of six years. There were some dietary restrictions imposed in 3 cases with little or no medication given.

Twelve cases (34.3%) were unimproved after the completion of twenty-four injections. Three of these unimproved cases were given further injections—2 carried to 30 injections and 1 to 36 with no improvement noted. At times experiments were made with a fairly rigid dietary schedule and alkalies were given in 7 cases with no appreciable change in the symptoms. Seven of this group were classified as obstructive lesions of a varying degree and were not improved at all. In 3 of these the symptoms appeared aggravated by the injections and 4 showed a weight loss. Three of the obstructive cases were subsequently operated upon, with one fatality due to pulmonary infarct.



Case 5

Case 5. A three months history of duodenal ulcer. Film at left shows duodenal deformity. The one on the right shows a normal duodenal cap after treatment with histidine. Symptomatic relief obtained after the third injection. A gain of 20 lbs. in weight—no diet or medication. No recurrence after 6 months.



Case 6

It might be mentioned that of these 12 cases showing no immediate improvement, 3 subsequently appeared to show definite improvement a week or so after the completion of injections, after being placed on a strict orthodox medical regime, where before the injections, such a treatment had been of no value. This suggests the possibility of some delayed benefit. The duration of symptoms in this group was the longest. These were for the most part those ulcers the most resistant to the forms of treatment and complicated by some obstructive phenomena in 7 cases.

#### SUMMARY

1. Peptic ulcers, non-obstructive in type with comparatively short histories, appear to respond best to

Case 6. A duodenal ulcer history of three years duration. The films show the deformed duodenum and its return to a normal appearance after 24 injections of histidine. Symptomatic relief obtained after the 15th injection.

histidine injection treatment. Gastric ulcers appear to show a more rapid improvement than do duodenal.

2. There may be value in its use in those re-activated ulcers previously operated upon and in marginal ulcers, or in those cases in which further surgery is contra-indicated. More cases of this type will have to be studied.

3. If proven to be of value after a proper observation period, the histidine treatment's chief benefit would appear to be in its elimination of dietary and medication regimes together with rather prompt and early improvement of symptomatology with no disagreeable local or systemic reactions.

4. While this treatment appears of value, it can be seen from this preliminary report and from other cases reported that there has not been a large enough number of ulcers so treated with a period of follow-up observation of length sufficient to draw definite conclusions as to the permanency of apparently beneficial results.

#### REFERENCES

1. Aron, E.: Recherches sur l'ulcère expérimental. Strassburg.
2. Mann, F. C. et al.: J. A. M. A., 73:878, 1919. Am. Jour. Surg., 75:208, 1922. Am. Jour. Surg., 27:409, 1923.
3. Mann, F. C.: Am. Jour. Surg., 7:453, 1929.
4. Aron, E., and Weiss, A. G.: Compl. rend. Soc. Biol., 112:15-530, 1935.
5. Blum, P.: Bull. General de Therap., 253, 1933.
6. Hessel, G.: Munch. Med. Woch., 1934, 81, 1890-1891.
7. Lenormand, J.: Action de l'histidine. Gazettes des Hôpitaux, 107:255, 1934.
8. Smithies, F.: Am. Jour. Surg., 237, Nov., 1932.
9. Bulmer, E.: The Lancet, 2:1276-1278, 1934.
10. Mitchell and Hamilton: Biochemistry of the Amino Acids, Monograph Series No. 48.
11. Volini and McLaughlin: The Histidine Monohydrochloride Therapy of Gastrointestinal Ulcer. Medical Record, April 17, 1935.

## ABSTRACTS

GARRETT, B. C.

"Congenital Hypertrophic Pyloric Stenosis." South. Med. Jour., 28:450-452, May, 1935.

In this disease, there is a spasticity as well as a hypertrophy of the pyloric muscle fibers. The disease generally appears between the second and fourth weeks, predominates in breast-fed babies, is eight times as frequent in males and in most cases affects the first baby. The signs and symptoms include projectile vomiting, visible peristalsis, palpable pyloric tumor, loss of weight and scanty stools during the first few weeks of life. The combination of a palpable pyloric tumor and visible gastric peristaltic waves is almost pathognomonic. The author believes that X-ray examination is a safe procedure and attaches importance to the presence of a blunt rounded pyloric end of the stomach and a 60-80% gastric retention.

The cases that respond to atropine or belladonna medication are those in which the spastic element predominates. Most cases, however, require surgical treatment, the Ramstedt-Fredet operation is a most satisfactory one, the expected mortality being from 2 to 4%. It is emphasized that the operation is not a true emergency one and that there should be adequate preoperative care consisting of parenteral fluids, whole blood, atropine, gr. 1/500 A.C., phenobarbital, gr. 1/8 to gr. 1/4, thick cereal feedings, and gastric lavage before surgery and occasionally before feedings. Post-operative care consists in keeping the baby warm, beginning fluids by mouth in 2 to 4 hours after the operation, hypodermoclysis where indicated, early resump-

tion of thick cereal feedings, atropine, and breast milk, and adequate general pediatric care. The operative technique is described and mention is made that subsequent laparotomies have shown a normal pylorus in many instances. Recurrence or latent complications are described as rare. A table showing nine points in the differential diagnosis of pyloric stenosis and pylorospasm is included in the paper. J. Duffy Hancock, Louisville.

CONE, ROBERT E.

"Sigmoid Diverticulitis and Urinary Tract Infection: Case Reports." South. Med. Jour., 28:535-536, June, 1935.

Although sigmoid diverticulosis is relatively common, its etiological relationship to urinary tract infection has been seldom reported. In practically all of these cases, the route was by direct extension from inflamed diverticula. The author presents three cases of *B. Coli* urinary tract infection which were coincident with and apparently the result of sigmoid diverticulitis. In each instance, there was prompt relief or marked improvement after successful treatment of the diverticulitis. While the route of infection may be ascending or by the lymphatics, the author favors the hematogenous route as most likely but admits that the rarity of cortical renal infection is difficult to explain. He suggests that the possibility of the intestine being the focus should be considered in all cases of stubborn recurrent urinary tract infections due to *B. Coli*. Gastro-intestinal X-ray will be of considerable aid in making the diagnosis. J. Duffy Hancock, Louisville.

## SECTION VI—*Abdominal Surgery*

### Bleeding Gastric and Duodenal Ulcers\*

By

D. PHILIP MACGUIRE, A.B., M.D., F.A.C.S.†  
NEW YORK CITY, NEW YORK

**A**LONG with perforation, hemorrhage is an extremely serious complication of gastric and duodenal ulcers.

Clinically, ulcers may be classified as follows: (1) *exulceratio simplex* of Dieulafoy, the follicular erosions of Cruveilhier, and also the punctuate erosions of Brinton; (2) the acute round, simple or peptic ulcer whose base is formed by the *muscularis mucosa*; (3) the callous ulcer whose base is covered with granulations and whose margins show the results of long-standing reactive inflammation with the walls correspondingly thickened; frequently, the base ulcerates through the *muscularis mucosa* with a tendency to perforate and adhere to the neighboring viscera; (4) the type that the Continental surgeons term 'ulcer gastritis or duodenitis' which is, at times, almost phlegmonous in character. We invariably associate an invasion of bacteria, usually the streptococci, with both the third and fourth varieties.

The occurrence of hemorrhage varies from approximately 25% to 30% in duodenal, and 20% in gastric ulcers (1). Von Bergman, whose view is shared by the highest English authorities, concluded that the mortality, under medical management, was 5% in an analysis of 2,000 cases of bleeding ulcers. Hurst (2), of Guy's Hospital, London, reported a mortality of 2½% which is even less than that of von Bergman. On the other hand, Finsterer (3 and 4) gave a mortality of 25% under medical management, with 50% having very massive hemorrhages. A mortality of 25% was reported by Chiesman among the cases admitted to St. Thomas Hospital of London for gross hematemesis and melena.

In the writer's opinion, these hemorrhages should be classified into four grades: (1) when there is a small hemorrhage or repeated small hemorrhages by bowel; (2) in which, the patient vomits blood repeatedly in small quantities, in addition to small amounts of blood by bowel; (3) a rather continuous vomiting of small quantities of blood each time, possibly accompanied by some bleeding into the bowel which is persistent and alarming to the patient, himself; and (4) the so-called massive hemorrhagic variety, in which, the patient suffers primarily from serious epigastric distress before hemorrhage ensues. In those cases of duodenal and gastric ulcers that are being treated, and

cases of marginal ulcer that are suspected, there need be little conjecture as to the sources of the bleeding.

Hemorrhages may also be classified according to the blood and hemoglobin count. In the first and second grades, the red blood count is above two million and the hemoglobin 50 per cent. In the massive and serious forms, the red blood count is less than two million and the hemoglobin is less than 40 per cent. The systolic blood pressure is above 80 in the first and second, and less than 80 in the third and fourth grades. When in doubt, it should be remembered that bleeding occurs in the following liver conditions, viz.: portal cirrhosis, spirochaetosis icterohemorrhagica, obstructive hepatic jaundice, malignant tumors of the liver, hypertrophic biliary cirrhosis, hydatid disease, acute necrosis, portal cirrhosis, carcinoma of the common duct, haemochromatosis, primary carcinoma of the gall-bladder, calculi of the external biliary system, and cholecystitis. Special emphasis should be given to the congenital obliteration of the bile ducts and latent cirrhosis of Rolleston because of the possibility of the same infection, causing the ulcer, might also bring about the cirrhotic change in the liver.

Hemorrhages may also occur from splenic diseases such as: Vaquez's disease, polycythemia, von Jaksch's disease, Gaucher's disease, and, most important of all, Banti's disease (splenic anaemia) when the hemorrhage is so profuse and alarming. Rolleston believed that the enormously distended vasa brevia ruptured into the stomach as a result of torsion of the splenic vein. This was due to the great bulk of the organ which resulted in massive hemorrhages. Hemorrhage may also be encountered in acute and chronic leukemias.

Hemorrhage may also occur in Meckel's diverticulum with aberrant gastric tissue in its wall, ulcerations of the small intestines, and, of most importance, in serious pathological changes in the appendix.

According to Gray, in his Textbook of Anatomy, the gastro-duodenal artery is a short but large branch of the hepatic which descends near the pylorus behind the first portion of the duodenum. At the lower border of the duodenum, it is divided into two branches, the gastro-epiploica-dextra and pancreatoco duodenalis superior. This is in close relationship with the common duct, anterior to the portal vein.

In the first, second, and third grades of ulcers of a single bleeding, the medical treatment of hemorrhage consists of the administration of a hypodermic of mor-

\*From the New York Post-Graduate Medical School and Hospital.  
†Assistant Clinical Professor of Surgery, Columbia University.  
Submitted April 11, 1935.

phine (gr. 1/6), and atropine (gr. one one-hundredth) which should be repeated in order that the patient may enjoy rest and quiet. Small quantities of ice water, about 200 to 300 c.c., each, of chilled ferric chloride (1-1,000) and also silver nitrate solutions (1-1,000), glucose solutions up to 50%, and adrenalin solutions may be introduced through a Levine or similar tube. If the stomach is distended with blood, a suction should be applied with a syringe or an evacuator in order to permit the gastric walls to contract.

Dr. Frank Smithies (5), Chicago, advised the following medical treatment for bleeding ulcers. Repeated doses of morphine are to be administered which should be given intravenously in shocked patients. He prefers the Thomas Bogg method of clotting and estimating of blood clotting time. In cases of vomiting, bleeding, and gastric distension, he advocates a thorough lavage with normal saline solution at 110° F., as suggested by the late Dr. Rodman. After a preliminary emptying by lavage, nothing should be given by mouth. For more than twenty years, Dr. Smithies has employed as a nutrient enema the following: 8 ounces of normal salt solution, 50 c.c. of syrup of glucose, and 50 c.c. of 50% alcohol, administered by the Murphy drip at body temperature which is given four times within 24 hours. He also advises the administration of fluids intravenously and per rectum to keep up the fluid reserve. In cases where bleeding continues up to 36 hours, he advocates operative procedure. Both Hurst (2a) and Smithies (5) prescribe the immobility of the patient by keeping him quiet in bed, reassuring him, and administering sufficient morphine and atropine (one 1/100 gr.) or morphine alone, to keep him drowsy. Whole blood transfusions of cross-grouped blood are advocated by Smithies for control of continued seepage or "non-spurter" bleeding (5b). Some Internists have advised the use of foods and liquids by mouth but both Hurst and Smithies disagree with this treatment.

Dr. Lester Unger, the transfusionist of our hospital who also advocates massive transfusions in these cases, has so thoroughly convinced the writer of the advisability of this method that he has consistently applied it in all such cases, in which, he routinely administered 1,000 c.c. of whole blood by transfusion with marked success. If necessary, this amount is repeated three times in cases of massive hemorrhages. In the desperate ones, Dr. Unger believes that, after severe bleeding, a chemical change takes place at the site of the hemorrhage causing imperfect clotting to occur which has an unfavorable effect on checking the bleeding. Consequently, in these desperate cases, arrangements should be made for three donors instead of the usual one. If the hemorrhage continues after the administration of the usual medical treatment together with the series of massive blood transfusions advocated by Dr. Unger, it is generally conceded that all conservative measures have been exhausted and operative procedures must be considered.

Hurst (2b) states: "I believe that the only indication for operation, in the acute stage, is the persistence or recurrence of severe hemorrhage whilst the patient is still fasting, especially in individuals past middle life with a long history pointing to the presence of a chronic ulcer and with arteries so degenerated that they are unlikely to contract sufficiently for satisfactory plugging by thrombosis."

In operative cases of hemorrhage, particularly the third and fourth grades, the procedure usually consists of two stages. In the first stage, under local anesthesia supplanted by cyclopropane, ethylene, or gas-oxygen, surgical intervention should be confined to the source of the bleeding. In the hemorrhagic ulcers of the duodenum, the three vessels that we should bear in mind are the right branches of the coronary or gastric, and the pyloric branches of the hepatic artery in the bleeding gastric ulcers and the gastro-duodenalis, a branch of the hepatic.

A complete excision should be made through the healthy tissues, even to a transgastric approach, in the gastric ulcers; if necessary, ligating the "bleeders" with mattress sutures controlling the gastric or pyloric branches. It may be necessary to cut through the gastro-hepatic omentum in order to mobilize the gastric area. After mobilization of the gastric area, an incision is made 1 c.m. distal to the pyloric ring. It is brought transversely across the duodenum, holding the superior and inferior angles taut by stay sutures according to the von Haberer technique. The incision should be sufficiently extensive so that the ulcer may be excised by a cautery of low heat. The base of the ulcer should be scarified according to von Haberer's technique and the bleeding kept under control. Then, the resected edges of the ulcer should be sutured together. The exclusion operations of von Eiselsberg through the pyloric ring, or Devine of Melbourne, above the incisura, require too much time in patients whose lives virtually hang on a thread. In the before-mentioned operative procedure, the time factor involves the necessity for furnishing a jejunal anastomosis. Again, unfortunately, it leaves the acid producing pyloric antrum intact.

In the Author's opinion, there is no question but that the operating surgeon has been unable to find the offending lesion in many cases and has encountered a general oozing condition which might have been due to extrinsic causes and not ulcers. In such cases, the gastric or duodenal area mucous surfaces resemble the appearance of a wet blotter. Faulty diagnosis was often due to an imperfect work-up.

In the third or fourth grouping that the writer has made, the condition to be dealt with is far more serious than the ulcer. This is a streptococcus invasion of the blood vessels, with all its attendant pathology, which reduces them to almost a gelatinous state obliging the surgeon to explore quite a distance to find an artery sufficiently healthy to clamp-off.

Out of every seven cases of massive hemorrhages, three are fatal according to Aitken (6) and 10 to 11% of the moderately severe ones.

In those cases, not reacting favorably to medical treatment and massive whole blood transfusions (3 if necessary), operative intervention is indicated. If the bleeding continues in a persistent hemorrhage from a posterior duodenal ulcer before a posterior duodenal approach has been made, it is advisable for the operating surgeon to pass his left index finger into the foramen of Winslow and attempt to control the hemorrhage by applying pressure so that he may orient himself. The writer has found that, by inserting his left index finger through this foramen and extending it under the gastro-hepatic omentum above the first portion of the duodenum, and making an incision in the omentum so that a rubber catheter may be passed through by

elevating the ends of the catheter caught by a Kelly clamp, the bleeding, in this area, may be controlled in most cases, except in those exceptional ones, in which, a collateral anastomosis exists with the gastro-epiploica-dextra artery. There is little danger of injuring the common duct since the Author has found it to be a very resistant structure. In experiments on the cadaver, his efforts to tear it after suturing in a rubber drainage tube were of no avail. Having controlled the hemorrhage, the next step is to make the posterior duodenal exposure and ligate the cause of the bleeding.

Some authorities have cautioned against transfusions in amounts greater than 250 to 300 c.c.. They believed that it increased the systolic pressure to such an extent, even up to normal or above, that further bleeding would be encouraged since tarry stools are sometimes seen even after a blood transfusion of 500 c.c. This is only a temporary condition and the blood added in large amounts is very beneficial to the patient. There has often been some question, in the Author's mind, as to whether blood transfusions in small amounts are really beneficial in serious cases since the patient is usually disturbed by the preparations for the procedure as is evidenced by the perspiration and the look of anxiety that appears on his face. Small amounts of transfused blood hardly compensate for this nervous state. Dr. Unger disproved the before-mentioned theory and further claims that the systolic pressure declines following repeated transfusions of whole blood, never coming up to normal, and is usually 10° to 20° below it.

Dealing with patients who are already mortally ill, it is not surprising that a mild, or even, severe alkalosis develops from a combination of alkalosis, due to the Sippy regime, a chloride formation of 2 gm. instead of 5 gm. according to Wildman, and a hemorrhage with intense vomiting. When the acid gastric secretion occurs in normal function, chlorine ions are withdrawn from the blood bearing an excess base which, combining with  $\text{CO}_2$ , increases the bicarbonate reserve of the blood. The base chlorine balance in the blood is re-established by the absorption of chlorides and water from the gastric juice in the ileum and colon. Alkalosis may result from any abnormality which prevents the absorption of the chlorides in the small intestine.

In the ulcer cases, particularly in the presence of an obstruction, there is a loss of gastric juice, which contains hydrochloric acid, due to the vomiting. This depletes the chlorine ion content of the blood.

The normal blood chloride level and blood volume may be maintained for a while by the withdrawal of tissue chloride and fluid which is actually responsible for dehydration. When this supply of tissue chloride has been exhausted, a hypochloremia develops which liberates the originally combined chloride base so that it unites with the  $\text{CO}_2$  which increases the bicarbonate content. Then, the urine becomes alkaline because of the markedly diminished chloride excretion and the presence of an excess of base ions. The occurrence of alkalosis in ulcers is evidenced by a low chloride level, a high  $\text{CO}_2$  combining power of the plasma, a marked increase in the non-protein and urea nitrogen, and an alkaline reaction of the urine.

The imperativeness for the recognition of this complication is evident. The benefit to the patient, derived from the transfusions, will be augmented when this

affection is cured by the intravenous injection of 5% glucose and saline solutions.

In these ulcer cases complicated by obstruction and vomiting, the Author firmly believes that many of the fatalities were mainly due to alkalosis and not to the hemorrhage.

A re-emphasis has been recently made by Dr. Wright\* who states: "that preclinical and even severe scurvy is frequently present but unrecognized in adults. Vitamin C is omitted from the diet for various reasons some of which include: poverty, individual dislike for the foods containing Vitamin C, faddist diets, and last but of considerable importance, diets imposed by the medical profession in the therapy of gastric and duodenal ulcers, colitis, and certain other conditions."

Using a standard capillary fragility test, previously described by Dr. Wright (7), it has been made possible to demonstrate that the capillary fragility is definitely increased in a moderate percentage of patients who have been on ulcer or colitis diets deficient in Vitamin C. At first, this is present without gross evidence of scurvy but is later accompanied by frank hemorrhage from the gums, intestines, and subcutaneously. Thus, such diets have been shown to definitely increase the tendency to hemorrhage.

This syndrome can be quickly cured by the use of crystalline Vitamin C (cevitamic acid) either orally or intravenously. The oral dosage should be from 60 to 100 m.m. given daily in divided doses. The amount, given intravenously, is 100 m.m. dissolved in 5 c.c. of normal sterile saline solution or distilled water. In a series of acute ulcer and colitis cases, this substance has been well tolerated when taken by mouth. In several instances, severe intestinal hemorrhage, ascribed to colitis, has been entirely cleared-up by simply adding this substance to the diet. Therefore, it is suggested that cevitamic acid should be included in all diets deficient in Vitamin G, particularly, in those conditions frequently associated with oozing or frank hemorrhage. It is candidly admitted that the use of this substance will not effect hemorrhages which are dependent on the erosion of large blood vessels. However, it may have a very definite influence on bleeding associated with changes in the smaller blood vessels.

Cases have been seen, in which, it is impossible to arrest the hemorrhages by the administration of repeated blood transfusions and the application of glucose and saline solutions. In order to build-up these cases to the proper condition for exploratory operation, the writer recommends repeated intravenous injections of liver extract from ampules (5 c.c.), the active and anti-anaemic principles, of which, are equivalent to 100 grammes of fresh liver. He also recommends the intravenous injection of glucose solution up to 50 per cent. The liver extract raises the hemoglobin and red blood cell count and both solutions are invaluable for the elimination of the hemorrhage. Further experiments with these injections will be reported at a later date.

Regarding the operation of choice for cases of ulcer in the vicinity of the pyloric ring, a modification of the Billroth No. 1 procedure, advocated and practiced by von Haberer in nearly 2,000 cases, is becoming very popular at the present time. There should be no devia-

\*Personal communication to the Author by Dr. Irving S. Wright of New York City, N. Y.



tion from this technique since he has perfected it to a high degree of efficiency.

The Hoffmeister-Finsterer type of operation is advised to deal with ulcers higher up in the lesser, or in the greater curvature or body of the stomach. We are all well aware that the higher the resection is made, the greater is the corresponding increase in the mortality in these cases.

In cases of the non-resectable type of posterior hemorrhagic duodenal ulcers, in which, it is impossible to cover the base of the ulcers by suture, the only hope of alleviation is by neutralizing the gastric acidity by a gastrojejunostomy as advocated by Balfour (8 and 9), who reports such cases of his cured to as high as 85 per cent, or, preferably, a gastrectomy, in which, the percentage of cure is 10% higher or better. During the period of operation, the mouth should be kept scrupulously clean in order to avoid the danger of parotitis. Hurst (2c) recommends 15 ounces of normal saline solution via rectum every 6 hours. Both Hurst and Smithies agree that it is necessary to wash out the stomach in cases of continuous hemorrhage.

After the patient has recovered and is in good condition, the second stage of the operative procedure should be performed which should aim at preventing a recurrence of the ulcer.

### CONCLUSIONS

From the surgical standpoint, the most important step in dealing with serious and persistent bleeding ulcers is to confine the operator's efforts to the arrest of the hemorrhage since the second stage of the operation eliminates the cause.

### REFERENCES

1. Wllensky, A. O., and Crohn, B. B.: Studies in the physiology and pathology of the stomach after gastro-enterostomy. *Am. J. M. Sc.*, 153:808-809, June, 1917.
2. Hurst, A. F., and Stewart, M. J.: Gastric and duodenal ulcer. London, Humphrey Milford, 1929.
- 2a. *Ibid.*: p. 269.
- 2b. *Ibid.*: p. 273.
- 2c. *Ibid.*: p. 276.
3. Finsterer, Hans: Die Bedeutung der Resektion zur Ausschaltung für die Behandlung des nicht resezierbaren Ulcus duodeni. *Wien. klin. Wchnschr.*, 46:545-549, May 5, 1933.
4. Finsterer, Hans, and Cunhn, Felix: The surgical treatment of duodenal ulcer. *S., G. and O.*, 52:1099-1114, June, 1931.
5. Smithies, F.: Notes on diagnosis and prognosis in gastric ulcer: A clinical study of five hundred consecutive, operatively demonstrated cases. *Am. J. Digest. Dis. and Nutrit.*, 1:697-704, Dec., 1934.
- 5b. Smithies, F.: The treatment of massive gastro-duodenal hemorrhage. *Am. J. Digest. Dis. and Nutrit.*, 1:803, Jan., 1935.
6. Aitken, R. S.: The treatment of profuse bleeding from the stomach and duodenum. *Lancet*, 1:839-842, April 21, 1934.
7. Wright, I. S.: Treatment of adult scurvy with crystalline Vitamin C (Ascorbic acid). *Proc. Soc. Exper. Biol. and Med.*, 32:475-477, Dec., 1934.
8. Balfour, D. C.: Surgical treatment in the bleeding type of gastric and duodenal ulcer. *J. A. M. A.*, 73:571-575, Aug. 23, 1919.
9. Balfour, D. C.: The surgical treatment of hemorrhagic duodenal ulcer. *Ann. Surg.*, 96:581-587, Oct., 1932.
10. MacGuire, D. P.: Gastrojejunal or marginal ulcer. *New York State J. Med.*, 35:161-164, Feb. 15, 1935.
11. Allen, A. W., and Benedict, E. B.: Acute massive hemorrhage from duodenal ulcer. *Ann. Surg.*, 98:736-749, Oct., 1933.
12. Hinton, J. W.: Fatal hemorrhage in peptic ulcer treated conservatively. *Am. J. Surg.*, 22:315-317, Nov., 1933.
13. Crohn, B. B.: Affections of the stomach. Philadelphia, W. B. Saunders Co., 1927.

## ABSTRACTS

MCNEALY, R. W. AND LICHTENSTEIN, M. E.

*Evolution and Present Technique of Gastrojejunostomy.* S., G. and O., Vol. 60, No. 5, May, 1935, pp. 1003-1015.

In a complete review of the history of gastrojejunostomy the authors show how experimental work in the laboratory has contributed to our present knowledge in that branch of surgery, and how trial and error in actual clinical surgery have contributed far more. The stoma of the efferent limb of the first gastrojejunostomy performed by Billroth was found to be obstructed because of a mechanical defect. Shortly thereafter many modifications of the operation were suggested. Woelfler, who had performed the first gastrojejunostomy in 1881, suggested stenosing the stoma of the afferent loop by suture, or removing the

No surgeon should consider operating on cases of acute ulcer complicated with massive hemorrhages, which are often primary, when the patient is in actual shock since most of the patients die on the operating table as a result of the low systolic pressure, hemoglobin and blood count.

Errors are seldom made in dealing with gastric bleeding ulcers, but this, unfortunately, is not the case in the duodenal variety. Small or already healed ulcers that appear on the anterior or superior surface of the duodenum are excised, following which, a gastro-enterostomy is performed. When the patient starts to bleed again several days following the operation, which the operator may ascribe to a marginal or gastrojejunal ulcer occurring post-operatively, he suddenly realizes his lack of foresight for not making a more thorough exploration of the area.

Von Haberer, whose technique is generally used on the Continent, incises the duodenum, transversely, clear across the anterior duodenal wall with a wire loop cautery. Exploration of the posterior duodenal wall can then be safely made with either a diagnostic lamp or the operator's finger since ulcers on the anterior or superior surface of the duodenum have seldom been known to cause a severe hemorrhage. The Deaver-Judd exploratory longitudinal duodenal incision is often used in this country.

Extreme care should be exercised when handling a cautery so as not to injure the pancreatic capsules. It should never be held at right angles, but flat to the surface being cauterized.

afferent limb entirely and suturing it to the afferent limb at a point beyond the anastomosis. That principle was later expounded by Roux in relation to posterior gastrojejunostomy. In 1885 the feasibility of performing posterior gastrojejunostomy through an avascular area in the transverse mesocolon was proposed from Billroth's clinic.

The posterior operation grew in favor and attracted the attention of many surgeons. It received a further stimulus by Peterson, who showed that it was possible to anastomose the jejunum to the stomach close to the duodenojejunal flexure without much tension. That obviated the necessity of a proximal loop, and made it unnecessary to perform the Y operation of Woelfler or Roux.

Among the factors contributing to the failure of those early operations, infection and its sequellae were outstand-



ing. Various devices were proposed to make an aseptic anastomosis possible; among them was the elastic band of McGraw, the heavy silk ligature of Postnikov and Podrez, the angiotribe of Souligoux, and the use of canstics by others. Failure of such cases was due to the closing of the stoma sometime after operation. In order to split the margins of the stoma and keep it open, various devices were proposed, among them were the decalcified bone plates by Senn in 1888, raw hide plates by Robinson in 1890, the button by Murphy in 1892, the bone-bobbin by Mayo-Robson in 1893, and in 1900 the perforated silver plates by Crede.

Physiologically the stomach has been divided into two large divisions, namely: the secreting portion, and the motile, grinding portion. The former is the cardia, fundus and body of the stomach, while the latter is the antrum and pylorus. Experimentally it has been found that the stoma of a gastrojejunostomy functions best when it is neither in the antral portion of the stomach, nor too high on the body. Considerable discussion about the exact position the stoma should occupy has brought some degree of general agreement. The location of the stoma in the small intestine should be on the antimesenteric side close to the ligament of Treitz. The lowest portion of the stomach will be found somewhere on the greater curvature between a point one and one-half inches proximal to the pylorus, and another point two inches from the mid-line. This lowest point in the stomach usually lies to the left of the mid-colic artery, but occasionally is to the right of it. There is no general agreement about the direction of the long axis of the stoma in the stomach. If the anastomosis can be made without kinking or twisting the small bowel, it will probably function satisfactorily. Moynihan stated that "just as there is no natural direction of the jejunum, so there is no best line for the anastomosis." Occasional variations in the anatomy of the stomach, duodenojejunal angle and transverse mesocolon will influence the exact location of the site of anastomosis.

Herniation of viscera from the greater sac into the lesser sac may be guarded against by suturing the edge of the hole in the mesocolon to the stomach, or to the line of anastomosis between the stomach and jejunum.

Increasing experience has shown that the use of absorbable suture material is probably most satisfactory. It is important that the sero-muscular suture include the submucosa also.

The Authors feel that the lock stitch is not satisfactorily hemostatic, if post-operative hemorrhage is to be consistently avoided.

Before the operation has been concluded a careful inspection and survey should be made to establish: (1) the correct arrangement of the anastomosis, (2) the absence of twists or kinks, and (3) the patency of the stoma.

Four figures and a large bibliography accompany the article.

Nelson M. Percy, Chicago.

CURRY, F. S., AND BARGEN, J. A.

*Studies on Absorption and Excretion in Segments of the Colon in Man. Surgery, Gynecology and Obstetrics, Vol. 60, No. 3, March, 1935, pp. 667-674.*

The authors studied the absorption and excretion of certain substances by the distal segment of bowel in a number of colostomized patients. The distal segment of the colon was cleansed until practically sterile. The test substance was instilled through a rubber catheter, and after a period of time the residue was recovered by irrigating the segment with 1000 cubic centimeters of water. This residue was then analyzed.

It was found that when sucrose was instilled into the bowel it was promptly absorbed and excreted by the kid-

neys. Following the removal of the sucrose from the bowel, urinary excretion of sucrose abruptly ceased.

When arsenic in the form of a solution of neoarsphenamine was instilled into the bowel in quantities of 0.6 gram it was excreted by the kidneys, and also by the bowel above the colostomy.

When glucose solutions were instilled into the bowel it was absorbed in each instance. In non-diabetic individuals the blood sugar value remained unchanged, while in patients with diabetes the blood sugar values were definitely elevated.

Methylene blue and atropine, when instilled into the distal segment of the colon, are absorbed.

It was found that methylene blue, when administered orally, was not excreted by the distal segment of the colon. Glucose and sucrose, when given intravenously, are not excreted by the distal segment of the colon. Arsenic given orally may be recovered in part from the distal segment of the colon.

Eight tables and a bibliography accompany the article.

Nelson M. Percy, Chicago.

ERNEST J. OESTERLIN, M.D., AND ROBERT W. BLUMENTHAL, Milwaukee, Wis.

*Spindle Cell Sarcoma of the Pancreas. (From the Pathologic Laboratory of the Milwaukee Hospital).*

Sarcoma of the pancreas is very rare. Gruber could not find one in 20,302 autopsies and Remo Segré mentions only two in 11,492 postmortem examinations. Notwithstanding the small number reported the authors state most of them cannot stand criticism.

Three types are described: Round cell, giant cell, and spindle cell sarcoma but Marxer found that many of the reported pancreas sarcomata are either lymphosarcomata, or metastatic tumors or not true blastomata but of inflammatory origin.

Litten's case which is quoted so often as the first described sarcoma of the pancreas was really a lymphosarcoma. The spindle cell sarcoma is the only type withstanding criticism and but only a few of these are to be found in the literature covering a period from 1890 to 1930.

The authors describe a case of spindle cell sarcoma of the pancreas admitted to the hospital for the first time in March, 1932, after several years of slowly progressing weakness. Six months previously he had a severe chill with fever and vomiting which anomalies recurred irregularly over the next three months. Following this he felt better for three months, gained 30 pounds in weight and returned to work. He again had fever, chills and vomiting preceding his return to the hospital. His abdomen then was rounded and no tumors or tender areas were observed. "The liver was 1 cm. below the costal margin; spleen not palpable."

*Laboratory findings:* Basal metabolic rate + 20%, blood Wassermann negative; blood culture negative; blood sugar 196 mg., non-protein nitrogen 38.7 mgms.; blood in feces, benzidine positive; guaiac and Rolland tests negative; electrocardiogram showed slight evidence of coronary sclerosis; r.b.c. 5,650,000; w.b.c. 18,300.

On the second admission (May 12) urobilinogen (1-8) was found in the urine but the test was negative five days later—then became positive again; three days later, just after operation, it was present 1-2, and increased gradually 1 to 100 June 1st. Then it came down 1 to 40 until he died June 4th. Bile pigment was constantly found in the urine. The highest temperature while in the hospital was 104° F., pulse rate 108, respiration 22. The urinary sugar ranged from negative to 4+.

*The exploratory operation* (May 20) revealed a greatly distended gall bladder, an enlarged but not nodular pan-

creas and an enlarged liver with rounded edges and irregular mreas.

*Postmortem examination:* Anatomie diagnosis: Pleomorphic spindle cell sarcoma of the pancreas. Its head was the size of a large grapefruit containing many cryptic cavities. The parenchyma was replaced by fibrous tissue which showed microscopically irregular whorls of pleomorphic cells with the coarse mature connective tissue fibres; spindle shaped cells predominated. There were occasional giant cells and scattered necrotic areas invaded by neutrophils. The spleen weighed 370 gm. There was acute splenitis. The liver weighed 2130 gm. and contained multiple abscesses; culture of the pus showing *B. coli*. Microscopic examination showed necrotic areas invaded by neutrophils. The periportal connective tissue and the bile ducts were much increased. The liver cells showed fatty degeneration.

The authors note the probability that the sarcoma of the head of the pancreas developed on a preexisting fibrosis.

Allen Jones, Buffalo, N. Y.

EDWARDS, H. C.

*Diverticula of the Duodenum.* S., G., and O., Vol. 60, No. 5, May, 1935, pp. 946-965.

Duodenal diverticula are classified by the Author as acquired hernial (or primary) type, those secondary to ulcer, traction diverticula and anomalous forms.

Of the author's five specimens, four are single and were found in relation to the ampulla of Vater (perivaterien). In the fifth, two diverticula were present, arising from the transverse part of the duodenum. A typical primary duodenal diverticulum is a thin walled sac opening into the bowel by a wide mouth. It rarely exceeds the size of a golf ball, and is rounded in shape as opposed to the finger-like congenital type of diverticulum.

The average age of the cases reviewed was 51.9; the oldest being 73, the youngest 31. Females are more often affected than males.

The diverticula were found most frequently in the second part of the duodenum, and were rarest in the first part.

The Author feels that the great frequency of diverticula about the ampulla of Vater is due to the weakness of the duodenal wall at that point. The common bile duct and the pancreatic duct of Wirsung pass obliquely through the duodenal wall for about one-half an inch. Along the course of those ducts there is a deficiency in the longitudinal musculature of the bowel. Deficiency of the muscular layer along the course of the blood vessels is not so marked. Increased intra-duodenal pressure resulting from obstruction, or, more often, from incoordination of contractions, results in a herniation through the weaker point, or points. The Author feels that a possible pre-disposing cause of increased pressure may be constriction of the transverse portion of the duodenum by the superior mesenteric vessels, or a sharp angulation at the duodeno-jejunal juncture as is found in most cases of visceroptosis.

Diverticula which develop upon old ulcers may be identified by the presence of the small scar, usually at the mouth of the diverticulum. They are found most frequently in the first part of the duodenum. The contraction of the dense scar tissue shortens and puckers the wall of the duodenum causing the ballooning out of the adjacent part.

Traction from an old adherent gall bladder, or common bile duct, may produce traction diverticula.

Pseudo-diverticula may result from perforation of duodenal ulcers into the peritoneal cavity. One case of diverti-

culum associated with a new growth has been described. Twelve figures and a complete bibliography accompany the article.

Nelson M. Percy, Chicago.

FINNEY, J. M. T., JR., AND MOHR, CHARLES F.

"Coronary Occlusion Simulating an Acute Abdominal Emergency." *Am. Jour. Surg. (New Series)* 28:622-639, June, 1935.

Three cases of coronary occlusion presenting purely abdominal symptoms are presented. While cases of this kind are rare, proper differentiation is most important since surgery, such a necessity in acute abdominal conditions, becomes a tragedy in this group. The usual criteria of the location of the pain, irregularity of heart action, drop in blood pressure, and electrocardiogram are often of little aid. All the pain may be referred to the abdomen, the irregularity of heart action may not show itself for some time, the drop in blood pressure may either be deferred or may have occurred before the patient was seen by his physician, and electrocardiographs are not likely to be diagnostic immediately. Other signs of cardiac failure are also often rather late in their manifestations.

A carefully taken present and past history is of extreme importance. The longer the history and the more severe and frequent the pain, the less likely is it to be cardiac. Males are four times more subject to coronary occlusion than are females. So far as age is concerned, the heart is more likely the offender after 50. In regard to the past history, the following points would rather incline to coronary occlusion: pre-cardiac discomfort, sense of constriction in the chest, appearance of pain after activity, tachycardia and irregularity of heart action, and dyspnea. While the abdominal pain in occlusion is often confusing, it is not so prone to radiate as in gall-bladder disease and the point of maximum tenderness is more usually found close to the midline. In spite of these differential points, the possibility of the disease must be borne in mind in order to recognize its presence.

J. Duffy Hancock, Louisville.

JELKS, EDWARD.

"Some Points in the Early Diagnosis of Gastro-Intestinal Cancer." *South. Med. Jour.*, 28:446-450, May, 1935.

Altho the recent decrease in mortality of cancer of the stomach is attributable not so much to improvement in surgical technique as to earlier diagnosis, there is still too much delay in the recognition of malignancy of the gastrointestinal tract. Emaciation, tumor, obstruction with persistent vomiting, and severe hemorrhage occurring in a person in the cancer age are indications of incurable malignancy rather than early operable lesions. There are, however, seven rather early findings. They are alternating diarrhea and constipation, recurrent attacks of vomiting long before complete obstruction occurs, indefinite indigestion which may or may not be related to ingestion of food, discomfort from distention in epigastrium or lower abdomen, anorexia, anemia manifested by paleness or dizziness, and unexplainable weakness. Briefly, any change in the gastro-intestinal life of an individual over 30 years of age may be an early sign of cancer and in those instances the burden of proof against cancer rests on the physician. Sigmoidoscopic examination of all patients with hemorrhoids and X-ray study and examination of the stool for both gross and occult blood in all patients with gastrointestinal complaints are recommended.

J. Duffy Hancock, Louisville.

## SECTION VIII—*Editorial*

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastroenterological Association is in no way responsible for editorial expressions.

### ON AN ADEQUATE CONCEPTION OF THE ETIOLOGY AND THE SIGNIFICANCE OF PEPTIC ULCER (GASTRIC AND DUODENAL)

IN 1917, writing upon the necessity for a broad conception of the cause of peptic ulcer as bearing upon its clinical management, we made the following statement: (1) "We cannot expect ever to establish a single, definite cause of gastric ulcer"; "likewise, it would appear that we have no basis for regarding gastric ulcer as a distinct disease entity," and "facts strongly suggest that peptic ulcer presents aspects indicating its being a self-limited 'disease.'"

In that particular communication, we proposed a mode of ulcer therapy which had, at least, the merit of attempting to be in line with known physiologic and pathologic departures from the normal where peptic ulcer was present.

In 1923 (2), the writer reaffirmed his position and amplified the mode of management which, after nearly six years' trial under careful control, had proved certainly not less efficacious than the "rule-of-thumb" treatment in vogue (chiefly over-alkalinization). In 1927 (3) and in communications subsequent to that year, the significance of known facts (physiological, experimental, chemical and clinical) was emphasized as they concerned treatment, not alone of gastric ulcer but also of the duodenal lesion. Schematic representations of what we considered mural concomitants of the peptic, gastric or duodenal, lesion, were exhibited and evidence was adduced to prove that by our "physiologic rest regime"—the *non-interference with natural healing*—a higher percentage of lesions went on to favorable clinical outcome than occurred when medical, "drug treatment," was pushed. Fuller data in this respect were submitted in 1932 (4) when we considered before the Section on Gastroenterology and Proctology of the American Association at New Orleans the limited clinical usefulness of so-called "gastric mucin" as an agent in ulcer therapy.

Today, after more than twenty years of a type of clinical experience which has been carried on in close proximity to observations at the operating table, the physiologic, pathologic, chemical, roentgen laboratories and in the postmortem room—we feel that an adequate concept of gastric or of duodenal ulcer lies in considering these lesions not disease, *de novo*, but in fact complications appearing when certain mural anomalies occur and when these so progress as to interfere with the normal nutrition or life of tissue from those zones, lumenward. The consequences are the development of areas of faulty structure which readily are digested whenever any proteolytic agent comes into contact with them.

malics occur and when these so progress as to interfere with the normal nutrition or life of tissue from those zones, lumenward. The consequences are the development of areas of faulty structure which readily are digested whenever any proteolytic agent comes into contact with them.

Such agents or combinations capable of causing local gastric or duodenal proteolysis are:

(a) *HCl plus pepsin plus "devitalized" tissue.*

(b) *Pancreatic juice (with or without bile) plus "devitalized" tissue.*

(c) *Certain bacteria possessed of ereptic characteristics which may be carried to visceral walls and there, when conditions are favorable, attack devitalized tissue (quite likely, such bacteria are those to which former investigators attributed great significance in ulcer production, particularly when, by blood or lymph streams, the organisms were transported from distant so-called "foci of infection" to places of lodgement in the walls of the stomach or the duodenum; where the bacteria remained viable, these "infectious emboli" primarily caused areas of mural infarction).*

(d) *In the presence of mural, circulatory disturbances of a degree sufficient to result in local tissue death or lack of normal defence, the lytic action upon such altered tissue of the peptid-splitting enzyme present in normal blood-serum (5).*

(e) *Potent capillary—or arteriole—spasms (in degree and character similar to those capable of bringing about marked circulatory disturbances or even "trophic" ulceration in severe grades of such affections as Raynaud's syndrome and allied disorders) where, locally in the visceral walls, superficially or deeply, areas of defenseless tissue appear upon which any of the already mentioned agents or mechanisms subsequently may cause proteolysis. Particularly important is this conception of one mode of ulcer production since (1) Reeves' micro-anatomic injection investigations demonstrated how scant are the arterial-capillary anastomoses in the very regions where ulcer commonly develops; (2) since Goto, Durante and others have produced ulcer readily by adrenalectomy and by interfering with normal innervation to the visceral blood vessels; and (3) since Schiff, and more recently, Cushing, have produced or called attention to peptic ulcers occurring where certain portions of the brain or the spinal cord are the loci of injury or disease. Of by no means trivial significance is the weight in ulcer etiology of disturbed innervation, with regards not just alterations in the quantity and kind of digestive secretion but more definitely in the production of mural circulatory defects of a grade capable of*

1. Smithies, Frank: Am. J. Med. Sci., Vol. CLIII, No. 4, 1917, April p. 547.
2. Smithies, Frank: Am. J. Med. Sci., Vol. CLXVI, No. 6, 1923, December, p. 781.
3. Smithies, Frank: Ann. Int. Med., Vol. 8, No. 10, 1927, April, p. 918.
4. Smithies, Frank: Am. J. Surg., New Series, Vol. XLIII, No. 2, 1932, p. 232.

5. Smithies, Frank: J. A. M. A., LIX, 1912, p. 539.

ending in structural anomalies. Further, fatigue or emotional upsets, of themselves, are being more widely recognized as responsible for actual organic damage in the stomach or the duodenal wall: these abnormal mental and psychic states are capable of setting moving a mechanism whose end-consequences are large or small areas of tissue death or lack of normal defense. Such chain of events may include increased adrenal secretion, potent and prolonged capillary or arteriole spasm leading to structural damage, alterations in duration and kind of digestive secretion, muscle "spasms" or disarrangement of normal peristalsis—in sequence or in degree—gravely interfering with normal, mural, blood distribution. Indeed, this aspect of the etiology of peptic ulcer now is being admitted so widely that today few considerations of the affection's management fail to specify the lowering of the patient's nervous, mental or psychic level, the lessening of the individual's "drive" in business, home, sports. Etiologic factors arising from the emotional make-up of ulcer subjects received scant attention when we stressed them in 1917.

(f) *Arteriosclerosis*, whether or not associated with arterial hypertension, undoubtedly is responsible for initiating certain peptic ulcers. Usually, such sclerosis is that which early involves the capillary bed and extends from there, heartward, to larger and eventually to major blood vessels. Detection of such type of sclerosis is difficult unless, at operation or at autopsy, one has available for study the excised ulcer or a segment of visceral wall. In such specimens, one has little difficulty in demonstrating, minute, multiple (usually eventually coalescing) or large, solitary areas of true apoplexy. Tissue death is prompt in the hemorrhagic zone and later, provided the bleeding is not actually fatal, gradually it includes all the tissue lumenward from the particular vessel involved.

Study of the walls of the stomach or of the duodenum of many individuals particularly persons who are very active, physically and mentally, reveals numerous areas where scar tissue has replaced zones of apoplexy but where, however, no submucosal or mucosal damage took place (as evidenced by peptic ulcer) because the ruptured arteries were not those which supplied those parts. Examination of other specimens (particularly in instances where, as an initial lesion, there appears an acute, perforating, "round" ulcer such as described by Craveilhier—"punched out and non-inflammatory") demonstrates apoplexy in major arteries lying just beneath the serosa. In these circumstances, within a period so brief as an hour, lumenward tissue death, hemorrhage and necrosis occur. The necrosed tissue promptly is digested, by *any* proteolytic agent present (commonly the normally secreted HCl and pepsin), through the entire visceral wall: the classic form of ulcer results. Usually it is fatal. It is folly to think that any non-surgical mode of treatment could have been of value in this type of ulcer: indeed, all too often, the promptest operative procedures are of no avail.

Craveilhier's type of ulcer, illustrates in an *acute and complete degree* the mechanism of all ulcer production or recurrence. In the chronic lesion, successive areas of tissue-proteolysis occur (the clinical "relapse") wherever devitalized structure arises when any of the causes mentioned becomes active. Quickly or slowly, the ulcer-area becomes larger, scar tissue re-

places normal mural architecture, deformity supervenes (obstructive in about 19% of instances), crater-like lesions may be seen (especially in the stomach where a thick wall admits of considerable "burrowing"; less commonly in the relatively thin duodenum); larger arteries may be opened or proteolysis "digests" gross mural structure and then appear such dramatic "complications" as massive hemorrhage or "acute" perforation of a chronic affection (histologically considered only, inasmuch as in a *time* sense the "chronicity" may include but a few weeks or months).

(g) *Congenitally*, from birth may be present anomalies of circulatory distribution or at times, the visceral wall (more frequently in the stomach than in the duodenum) may include "tissue rests"—as those pancreatic rests described by the late Dr. Warthin. In such circumstances, the structural fault may be exhibited in infancy. Just so soon as the viscera are put to digestive stress, demands are thrown upon the circulatory mechanism, the normal secretions are elaborated and neuro-motor activity required, the defective architecture permits mural necrosis; proteolysis—"digestion"—follows and, in the infant or the very young, long before emotional "keying-up" or physical or mental "drive" has opportunity to develop, peptic ulcer symptoms and signs occur, not rarely as initial hemorrhage or perforation. Here, indeed, is the clean-cut occurrence of gastric or duodenal ulcer from intramural defects and long before "hyperacidity," "corrosion" (a term dating back to Celsus, later to be revived by Müller) or "the impact of the acid chyme upon the alkaline-bathed duodenal mucosa" have opportunity even to be regarded seriously as etiologic factors in ulcer production. Doubtless, more careful study of the structural, mural defects of the stomachs and the duodenums of the new born or of infants would prove most illuminating in respect to elucidating the significance of mural anomalies as later they occur more or less regularly in the adult viscera, whether such common birth defects are or are not complicated by the clinical symptoms or the outright appearance of peptic ulcer.

(h) It is not improper and certainly not valueless, here to consider so-called "*gastritis*" or "*duodenitis*" with regard to its bearing upon the etiology of peptic ulcer. Not rarely, such lesions precisely mimic the clinical picture of gastric or of duodenal ulcer: in fact, all too often, despite the absence of positive X-ray evidence, gastritis or duodenitis long is treated medically as ulcer and, in instances where symptoms persist despite carefully planned and long-maintained "ulcer" regimens, surgical intervention takes place: of course, no ulcer is demonstrated. However, in our experience, even though no localized "peptic" lesion is found, such surgical intervention (or, where untoward complications prove fatal and autopsy is secured) by no means is worthless if one looks upon the laparotomy as "exploratory" not just in the sense of proving that ulcer is or is not present. The "exploration" should be carried far beyond the search for ulcer or for extra-alimentary canal pathology.

In these "*gastritis*" or "*duodenitis*" patients, our observations have shown that by inspection, palpation, and particularly by transillumination of the stomach and the duodenum by an appropriate electric light, often it is possible to demonstrate the following: (1)

localized or general thickening of the visceral wall, (2) local or general areas of vascular engorgement or of anemia, (3) "stiffening" of segments—or, indeed, the entire stomach or duodenal wall; especially is this pronounced in the so-called "ulcer-bearing" areas; (4) the irregular scattering in the deeper (*i.e.* towards the serosal surface) layers of the wall of more or less definite plaques or zones of induration which feel scar-like compared with the normal mural softness and elasticity. These, upon transillumination, actually are definitely, or poorly circumscribed patches of induration due to vascular engorgement or scar formation: in fact, certain of these areas may extend to the serosa and then are comparable with the scarred "soldier spots" seen in certain hearts or aortas; (5) should the viscera be incised (as in the case of transgastric incision for posterior wall ulcer or search for such), the mucous membrane frequently is very thick, oedematous, congested; islands of such tissue are present amid areas of normally appearing membrane. While these islands may even bleed on handling or upon brushing firmly with a cotton applicator, no true ulceration is demonstrable: the mucosa, even tho very evidently abnormal, not yet has lost its protective vitality and acid and pepsin or other proteolytic agents are incapable of "digesting" it. The mucosal disturbance evidently arises from circulatory or even sluggish inflammatory processes lying deep (serosa-ward) in the visceral wall.

(i) Ingenious and painstaking as have been the *experimental methods* whereby have been produced peptic ulcer (duodenal and gastric, tho by far more numerous the former), the following facts must be recognized when interpreting the real significance of these artificially produced ulcers: (1) few ulcers, indeed, have been produced experimentally in animals in which "spontaneously" arising ulcers—as seen in the human—are of common occurrence; (2) in the production of experimental ulcer in animals, quite uniformly, the technique of production has upset the normal circulatory, secretory, nervous or even the anatomic relations of the parts involved; (3) even the most assiduous and careful experimenter has found great difficulty in producing the "chronic" ulcer, the type *spontaneously* developing in humans; (4) study of the stomachs or the duodenums of animals in which, experimentally, ulcers have arisen do not disclose such mural areas of defective circulation, infection, thickening, scar formation or neuro-muscular anomalies commonly observed in humans in whom peptic ulcer arises without such abnormal anatomic, secretory, nervous or muscular sequence as experimentation demands before ulcers are produced or maintained; (5) most recent investigations upon animals, would indicate that in such animals—subjects who rarely, if ever, develop the spontaneously appearing peptic ulcer of man (few monkeys, have been the subjects of experimentation: monkeys, structurally if not dietetically, are nearest akin to man)—some chemical "humoral" agent, regulates in a yet unknown way, the initiation, the duration and, perhaps, the quantity and "strength" of the output of gastric juice and probably the duodenal digestive content. In other words, this form of mechanism during the digestive process, in experimental animals, at least, controls beginning of digestion, the qualitative or quantitative values of the digestive juices and, not yet wholly proved but suspected, the

neuro-motor activity. If this concept be correct, much that is concerned with digestion (and absorption) from the time food is taken into the mouth is self-regulated in accordance with the kind and quantity of pabulum by successive "humoral" (a term generally understood in effect, but actually one which hides our ignorance of actual facts) sequences beginning even before food really is ingested and exhibiting itself in orderly fashion from the mouth down even to include happenings in the colon. Disorganization of these normal "humoral" sequences, may, of themselves, lead to quantitative secretory and motor anomalies in the digestive (and, probably, the absorptive) function. While the chief result of interference with these normal sequences may come through psycho-neural pathways, the manifestations of this activity account for changes from the normal in quantity and quality of digestive juices, duration in which food being digested remains in the stomach, or duodenum or jejunum, and, doubtless, variations in the rate of absorption. Whatever may be the provable variations from the normal so far as digestion is concerned, the *result* of the abnormalities is an interference with the normal "humoral" sequences which, in proper circumstances, make the digestive process an auto-regulatory mechanism. In the experimental production of ulcer, undoubtedly, much of this psycho-neural interference with digestive sequences of an "humoral" character is lost. Further, in the normal life of the average animal used as an experimental subject, such psycho-mural processes doubtless rarely are active and what, in a way, may be an etiologic cause of spontaneously arising peptic ulcer, never becomes operative—hence, again, one finds here the lack of a mechanism which lack seriously interferes with the comparison of experimentally produced ulcer with that appearing without recognized gross existing cause, in man.

#### SUMMARY

Careful histo-anatomic, clinical, pathologic and chemical studies, correlated from the time when peptic ulcer first attracted the attention of clinicians to the present day, indicate that the lesion arises "spontaneously" in the human family and in no other groups of living creatures.

Investigations point to *various agents or circumstances* as being etiologic factors but the *basic mechanism* of ulcer production (gastric and duodenal) evidently consists in disturbances in normal, mural, arterial blood circulation. Such disturbances occur almost universally in the walls of the stomach or the duodenum but only when they prevent free arterial blood-flow to a segment—large or small—which *includes the mucosa*, does ulcer follow: then, tissue, dead or lacking some yet unknown protective attribute, undergoes proteolyses and the peptic lesion appears.

The proteolytic agents are numerous but commonly consist of nothing other than normal digestive juices digesting defenseless tissue after the fashion in which they would attack protein as it occurs as part of a meal in the *lumen* of the viscus. Proteolytic agents other than normal digestive secretions have been listed and commented upon. The extent of proteolysis—and, hence, the size of the initial ulcer—is limited by the quantity of defenseless tissue available. Recrudes-



cences occur on a basis similar to the appearance of the initial "peptic" lesion. Thus, it follows, that in extent, persistence, severity and clinical attributes (hemorrhage, obstruction, deformity, perforation) the lesion is more or less "self limited."

In the walls of stomachs and duodenums where the proteolytic process has not involved the mucous membrane and, hence, no ulcer has occurred, usually can be demonstrated by histo-pathologic changes at microscopy and grossly by sight, palpation and transillumination, areas of congestion, tissue-lysis, scar production, deformity, in all respects resembling what occurs in true peptic ulcer, with the exception, however, that mucosal destruction has not developed and given rise to so-called "peptic" ulcer. The mural affection has healed and has been confined wholly to the wall. The older the individual, usually the greater is the number of these mural lesions—"scars"—which can be ob-

served. However, age is not a requisite for the appearance of such changes: in infancy, childhood and youth where local circulatory, neural, muscular or intra-mural localized infections or traumata have occurred, similar tissue defects can be demonstrated; at times they include the mucosa and are the fore-runners of peptic ulcer.

*Seriously and broadly considered, peptic ulcer is not a disease, sui generis. It is a complication of a prior mural defect due to many agents acting to produce arterial, circulatory defects. Whether or not these defects involve the mucosa and then are followed by the ulcer complication is accidental. Evidence is available which proves that the large majority of the human family experiences these mural defects but that such never include the mucosa and, hence, the large majority of the human family never develops peptic ulcer.*

Frank Smithies.

## SECTION IX—Book Reviews

(This section is open to contributions from any medical reader, whether a member of the Editorial Council or not).

*The Patient and the Weather, Vol. 2, Autonomic Dysintegration*, by William F. Petersen, M.D., with the assistance of Margaret E. Milliken, S.M. Published by Edwards Brothers, Inc., Ann Arbor, Michigan, 1934. 530 pages, 8½x11¼, price \$6.50.

**F**OR many reasons, this is a very interesting volume. In the first place, it is the most beautiful example we have seen of the new method of reproducing a type-written manuscript. The result is so satisfactory that it is to be hoped that in the future more books will be produced in this economical way. It would make possible the publication of many highly technical monographs which for economic reasons cannot now be printed in the usual way.

This is the second of a series of four volumes. The writer's thesis is that most diseases of the body are influenced by the weather. Wisely he admits, on the first page, that "other interpretations are possible and indeed probable. Seldom is one environmental factor alone responsible in a mechanism so complex as the human body. We deal with a constellation of events—but in this constellation of events the meteorological environment is probably the most important."

Dr. Petersen frequently uses the term "autonomic dysintegration" which may perhaps prove useful in the future. It may be an apt way of describing what takes place in many now poorly understood diseases. There is much evidence also in favor of the idea that many distressing upsets in health appear when they do because the patient is passing through a certain phase of one of many cycles which normally take place in the body chemistry. These cycles seem to be much more marked in females than in males. It is an impressive thing to go into a laboratory such as Slonaker's at Stanford or Richter's at Johns Hopkins where the movements of scores of white rats are being recorded every hour of the day and to see the remarkable peri-

odic variations in the activity of the females. Similar cycles of various kinds have been found in women, and it does seem reasonable to suppose that an attack of migraine or paroxysmal tachycardia or an epileptic seizure should coincide with some phase of one of these cycles of metabolism.

It has been known for ages and it has been shown scientifically by Rowntree and others that in some persons painful attacks of arthritis come with certain changes in weather, and it seems reasonable to suppose that careful study would show that other diseases are similarly influenced. Most openminded physicians are likely to feel receptive to such a thesis, and they would be interested to see what could be done in the way of proving it. Unfortunately, it has not been easy in the past to correlate arthritic pains with any particular meteorologic change. The impression the reviewer has had is that the body answers to some change in its surroundings which are not yet being detected or measured by any meteorologic instrument.

Even a cursory inspection of the volume before us will show that Dr. Petersen has attacked his problem with tremendous energy and perseverance. He has gathered and graphed an enormous mass of data, and one wonders how any one man could have read so widely and done so much research in so many fields. The cost also of the blood chemical work done must have been tremendous. For instance, on page 462, one finds 17 curves plotted one above the other, besides six meteorological records. The experiment was carried on daily from the 20th of April until the 15th of July on a patient with arthritis. Anyone who has ever attempted to carry out such a study knows what a time-consuming and costly job it is, and how large a force of laboratory helpers it requires.

Unfortunately, we fear the reader will feel rather appalled at the plethora of material. Certainly the reviewer feels that it would be impossible for him to ap-



praise the value of the volume or to form a safe opinion of the correctness of the author's theorizing unless he could spend several weeks analyzing the curves and studying the text. The reviewer's feeling is that the author would have created a much better impression and would have had many more readers and much more examination and discussion of his views if he had not offered so much material and had not claimed so much for so many diseases. It seems also as if he should have, in each case, briefly pointed out what the graphs show or prove. The reviewer fears also that in many cases the experiment was too short to prove much. Dr. Petersen presents scores of short charts showing that an attack of this or that occurred coincidentally with some meteorological event, but the reader must wonder if it would do this several times running, and would it fail to do so with the opposite type of weather?

We all tend to remember our hits and to forget the misses, and nowhere is this tendency more dangerous than in a work like this.

Another thing that throws doubt on the value of the book and makes it less easily read is the inclusion of many subjects which one does not expect to find here. For instance, it is hard to see what eclampsia and premature delivery have to do with weather. It is possible, as Dr. Petersen says, on page 204, that the weather precipitates attacks when the individual is conditioned by certain meteorological conditions, but it seems to the reviewer that a wise man would not dilute his best arguments by including a lot of weak and unlikely and unconfirmed theories. He who expects to have his writings read, especially in these busy days, must be brief, and must leave out everything that is not pertinent to his subject.

The reviewer has the feeling that Dr. Petersen's book is a wonderful quarry in which one might profitably dig. A better salesman would have taken out of this quarry his most beautiful bits of marble and placed them in logical order and clearly labelled in a small booth by the wayside where every passerby could see them with ease. It is one of the tragedies of this world that some of the hardest workers in science, men sometimes with unusual and original minds, and an enormous knowledge of the literature, fail to get a hearing or to influence the work of their fellows, simply because they write up their results so poorly or so unsystematically, or so vaguely, or so verbosely, or with such an admixture of chaff that other men throw up their hands in despair and say, "He is doubtless a genius and there is probably much in his writings which is of value, but I haven't the time now to search through his papers to see what is there." Such a man ought to stop every little while and get a trained editor to sit down with him for a week or two to put his writings into easily understandable form. He should get some one to show him where he is leaving out large gaps in his descriptions of work done, or gaps in his reasoning, to interpret him to the public, and to keep him from filling his papers with material which, although of interest and perhaps well enough written, does not belong where it is, and only brings confusion and boredom to the reader.

In spite of anything unfavorable that may be said of the plethora of data in this book, this reviewer has been sufficiently interested by it to hope that Dr. Petersen will supplement it with a shorter essay, based on his great work, and having as its purpose evaluation and interpretation.

Walter Alvarez, Rochester, Minn.

#### *Preview of Dr. B. B. Vincent Lyon's "Atlas"*

IN the Scientific Exhibit at the recent meeting of the American Medical Association we saw one demonstration which should be brought to the attention of our readers who are interested in the very difficult field of microscopy—and its interpretation—of material recovered by duodenal drainage of the biliary tract. We learned that from that exhibit soon there will be available an "Atlas" compiled by no less an authority than Dr. B. B. Vincent Lyon, himself.

This "Atlas" will be purely clinical in motive and scope. Over many years, Dr. Lyon, carefully and assiduously has made photomicrographs of characteristic and unusual cellular, crystalline, infectious, parasitic, etc., sediments and has correlated them with clinical and pathologic data. The scope of the work is tremendous. Practically every known gall-bladder and biliary tract condition has been covered. Most faithful photomicrography has been done. The advance sheets of this work reveal a series of actual photographs of the greatest interest and value. The accompanying descriptive text has been written by Dr. Lyon from the data in his own and others' archives; it presents a mass of really authoritative information compressed into an extremely brief space.

According to the schedule now set, Dr. Lyon's "Atlas" will not be available for distribution for about three months because of the immense amount of work required to make and mount the microphotographs (each is an "original") and to group and bind them in logical clinical sequence. What such a "different" Atlas can be sold for, of course, is problematical. In any event, the number of Atlases issued of necessity will have to be limited, since each volume is almost entirely hand-work. It is to be hoped that the cost per volume can be kept as low as twenty-five dollars: certainly, at such low price, it is our opinion that the books which become available, eagerly will be spoken for by clinicians who wish to do biliary tract drainages scientifically and purposefully. Even at double the mentioned price (no profit can accrue to the Author at such charge) the proposed Atlas will pay the purchaser big dividends on the investment.

Our profession could benefit greatly from the type of publication proposed by Dr. Lyon: what all of us need is not text-heavy books, largely constructed as "compilations" and illustrated by pictures as familiar to us as are those in the "Jack-and-Jill" books of our childhood. We need before us those facts, observations and data upon which important clinicians actually depend in their day-by-day diagnostic and therapeutic efforts.

Frank Smithies, Chicago.

## SECTION XII—"The Clinic"

### Typical and Atypical Terminal Ileitis

By

A. GALAMBOS, M.D.\*

and

W. MITTELMANN, M.D.

NEW YORK CITY, NEW YORK

**"TERMINAL** ileitis" or "regional ileitis" designates a condition described in 1932 by Crohn, Ginzburg and Oppenheimer as a "non-specific granulomatous inflammation of the terminal ileum."

The disease is a well defined ulcerative enteritis, in the greatest majority of the cases restricted to an average extension of about ten inches of the terminal portion of the ileum. This process is followed by a disproportionately marked chronic inflammation or connective tissue reaction in the covering submucosa, muscularis and serosa, producing a striking thickening of the wall of the gut, with a subsequent narrowing of the lumen, which results in stenotic or even in obstructive symptoms. The involvement of the serosa leads at times to ascites, more often however to an adhesion formation between the ileal coils, or between the small and large intestines as well as between the intestines and abdominal wall. The very marked tendency to a characteristic fistula formation, producing communicating fistulous tracts among the organs involved, viz.: the ileum, colon, abdominal wall, retroperitoneal tissue, should be emphasized.

The granulomatous infection secondarily involves the mesenteric glands. The thickened, strikingly infiltrated mesentery acts like a retroperitoneal mass, fixating and inhibiting the free peristaltic movement of the thickened ileum, huddling it into a mass, producing the manifestations of an apparent adhesion, when, often there is no peritoneal adhesion actu-

ally present. It is instrumental in producing outside of adhesions, secondary break-downs of the tissues, suppuration, retro-and intra-peritoneal abscesses and fistula formation.

The underlying *pathology* may lead to a palpatory finding of an indefinite resistance, or of a large inflammatory tumor in the area involved.

The macroscopical appearance and the microscopical histological findings in the resected specimen are uniform and pathognomonic, often only *per exclusionem*.

The *X-ray examination* reveals more details and characteristic hints than does the physical examination. In well defined cases, the diseased area is marked by a large filling defect, with a typical "string-sign," representing the direct visualization of the stenosed lumen of the terminal ileal coils. Fistulous tracts may similarly give a resemblance to the string-like appearance on the films.

The main points in the *history* of the case are: the age of the patient, the protracted course of the disease, diarrhea, undefined pain, occasional fever, slight leukocytosis, secondary anemia, tendency toward fistula formation, failure of previous appendectomies to improve the condition.

It is interesting to note that practically all the patients who came under observation were young adults. The question arises as to the fate of these patients as they arrive at old age. If we disregard the quite improbable outcome of a complete resorption, except probably in its earliest stage, one is forced to the conclusion, that all these patients die before reaching old age.

*Early recognition* of the condition is urged, because early diagnosis followed by adequate surgery (resection), leads, as a rule, to a cure, while a failure to recognize the disease results in chronic marasmus, leading eventually to a fatal outcome.

*Incorrect diagnosis*—as the history of most of the cases proves—often leads to unnecessary appendectomies, failing to afford any relief to the patient's condition, in fact, often preparing the way to a secondary fistula formation.

One of the *causes responsible for the failure to recognize the ailment*, in our opinion is due to the fact, that the X-ray examination of the ileocecal region is performed routinely, six hours after the barium intake, . . . at a time when the terminal ileal coils in that particular area are as a rule empty already. The X-ray examination will reach no conclusion, and "negative findings" will be reported.

Instead of the routine X-ray examination with a fixed standard time of six or twenty-four hours, it would be more correct to have an *X-ray study* instituted using *varying time intervals*, and *varying technic*, dictated by the individual needs of the case. As an instance in both of my cases the routine six hour examination produced diagnostically irrelevant pictures. In the first case, the films taken two and three hours after the barium intake, in the second case the thirty-six hour pictures proved to be most decisive and diagnostically most important. As a rule, the two, three or four hour exposures will prove to be of the greatest value.

\*Formerly Associate in Medicine, Royal Hungarian University of Sciences, Budapest.  
Submitted March 30, 1935.

The disease does not seem to be extremely rare. Crohn reported in his first series in 1932 about 14 cases; two years later the number of cases referred to was 42. Kantor mentions six cases in his paper. We ourselves diagnosed terminal ileitis in the last ten months, three times. Two of this series already underwent an operation and the operative and pathological findings proved the correctness of the diagnosis.

In all of our cases diagnosis has been made pre-operatively, in fact, in the first case strong suspicion has been expressed for this diagnosis, even before the X-ray examination has been performed.

### CASE REPORTS

Case 1, refers to a 42 year old white female, first seen at my office the 13th of March, 1934. She had diarrhea, of 15 years' duration. Her disease had a slow onset, and a slow progress. She had 3-4-5 mushy bowel-movements daily, without a noticeable admixture of pus, mucus or blood. She had no tenesmus, but she noticed an occasional periumbilical griping pain during defecation.

There was a more marked loss of weight during the last two years. She was beset by chills and fever (to 102 F.), of a few days' duration, once in every few months. Her general feeling during the intervals was quite satisfactory. Her doctor diagnosed these febrile attacks as "grippe." Her loss of



Fig. 1. Case 1. Terminal Ileitis. Typical case. Two hour film. Note the "string-sign" (arrow) and the "filling defect" in the ileocecal area. (Other parts of the G.I.T. are visualized by previous Ba. intake).

weight during the last 6 months was between 20 and 25 lbs.

On the 29th of July, 1933, patient was suddenly taken severely ill, with chills, fever and periumbilical pain and was rushed to a Brooklyn hospital,

where appendectomy has been performed. Patient remarks, that according to her surgeon's description the appendix removed has been found normal, but he noticed during operation certain unusual puzzling anomalies over the small intestines. The latter looked "swollen," like "sausages," or, resembling typhoid intestines. Between the appendix and sigmoid, retroperitoneal abscesses were found. They were opened and drained. Patient left the hospital after three weeks, and felt all right for the next three months, when the surgeon had to open the abdominal wall and drained externally an intestinal fistula. Patient felt generally comfortable as long as the fistula drained freely, but, as soon as it became blocked up, symptoms appeared. The surgeon had to intervene four more times to reconstitute and assure free drainage.

Her history was otherwise irrelevant.

On physical examination the abdomen showed spontaneous tenderness, which increased either upon touch or on examination even through the vagina or rectum. In the right lower quadrant there was a large indefinite mass palpable. The extreme sensitiveness of the abdomen decreased the following day, after the fistulous tract—incidentally just blocked—opened spontaneously, and drained pus again, freely. Presence of post-operative sear and fistulous tracts completes the findings over the abdominal wall.

Urine contained traces of albumen, with a negative findings in the centrifuged sediment. Feces gave slightly positive reaction for occult bleeding (Weber test). Hemoglobin was 58%. White blood count was 15,500, with 88% polymuclear, 7% large mononuclear cell, and 5% lymphocytes. The temperature on the first day of examination, when the fistulous tract failed to drain, was 102° F. The following day, after it broke open, temperature dropped to normal, pain subsided, white blood count fell to 14,000, with 72% polymuclear, 8% large mononuclear cells, and with 20% lymphocytes. The discharge consisted of a copious, odorless, thin and purulent material.

On account of this unusual history and physical findings, strong suspicion has been expressed as to the possibility of a terminal ileitis, and the subsequent X-ray examination served to substantiate this *a priori* diagnosis.

The X-ray examination of the gastrointestinal tract revealed the stomach, duodenum, jejunum and colon to be normal. All the pathology present was confined to the ileum.

The right lower quadrant of the abdomen was grossly characterized by a large filling defect of the ileal coils. The "string-sign" (Crane-Kantor) was demonstrated on all the films. It was interesting to note that the very last portion of the ileum in a length of 1-



Fig. 2. Case 1. On both the upper and lower films, the "string-sign" and the "filling defect" manifest marked similarity to the picture of the previous figure. "String-sign" (arrow) proved at operation to be the direct visualization of a narrowed ileal lumen and not an ileocecal fistula. All other pictures are nearly identical.

1½ inches was visualized as fairly normal. The proximal loops were not visibly distended. The 6 and 24 hour pictures were "negative," i.e. no visualization of the terminal ileal coils, nor of the proximal loops was demonstrated, evidencing the absence of an ileal obstruction. Films taken 2 and 3 hours after the barium meal proved to be the most convincing, visualizing the narrowed intestinal lumen ("string-sign"), with an otherwise failing filling of the other ileal loops (Stierlin's sign).

On re-operation, a sixty (60) inch portion of the terminal ileum, the cecum and two-thirds of the ascending colon have been removed, and an anastomosis between the ileum and the middle of the transverse colon instituted. The removed small intestine's wall was very thick, and its lumen greatly narrowed. No abscess was found at that time. The external fistula led into the ileum, four

inches above that valve of Bauhin. The string-sign proved to be a narrowed ilcal lumen, and not an ilcoecal fistula.

Patient made an uneventful recovery, and is today, ten months after the heroic operation, in perfect health.

Case 2, a female, white, aged 45, who was referred to me by Dr. Bela Mittelmann, on the first of December, 1934.

Her symptoms started eight years ago, with pain in the right lower quadrant of the abdomen. An operation for appendectomy in 1931 failed to relieve her suffering of years' duration. According to the description of the patient, the surgeon upon opening the abdomen was puzzled by certain unusual adhesion around the small intestines and the ascending colon. In the following year (1932) patient suffered from severe "heart-burn" during a period of two months. Then she was seized by severe abdominal pain, which after a few days' duration terminated with a gastric hemorrhage and melena, the latter allegedly present for two months. Patient, thereafter, has been taken to a leading hospital for a thorough examination, including an X-ray study of the gastro-intestinal tract. During a stay of eleven days no peptic ulcer has been found, and no definite diagnosis has been stated. Ulcer diet (Sippy's), and ulcer treatment, instituted several times always proved of no avail, in fact, the patient felt worse under strict regime.

Subsequent condition of the patient in the following period until six months ago was satisfactory. In September, 1934, she was seized by severe abdominal pain, necessitating her confinement to bed for a week or so. Ever since patient never felt quite well. She was losing weight in the last six months between 20 or 25 lbs. She felt a burning sensation in the throat, bad taste in the mouth, had anorexia, occasional vomiting, diarrhea, or a tendency thereto, with two or three mushy stools daily.

Physical examination was irrelevant, except for a moderately tender resistance felt in the cecal region.

Gastric analysis revealed complete achylia gastrica.

X-ray examination of the gall-bladder showed normal shape and function of that organ.

X-ray examination of the gastro-intestinal tract revealed normal stomach, duodenum, jejunum and colon. No signs of a chronic peptic ulcer has been detected. The pathology found referred solely to the ilcoecal region. The ilcal coils huddled into a mass, in the right iliac fossa, showed upon repeated examination, even on the 36 hour films, the picture of a permanent visualization, nearly identical on all the films. A very marked motor delay, pointing to the presence of an obstructive process

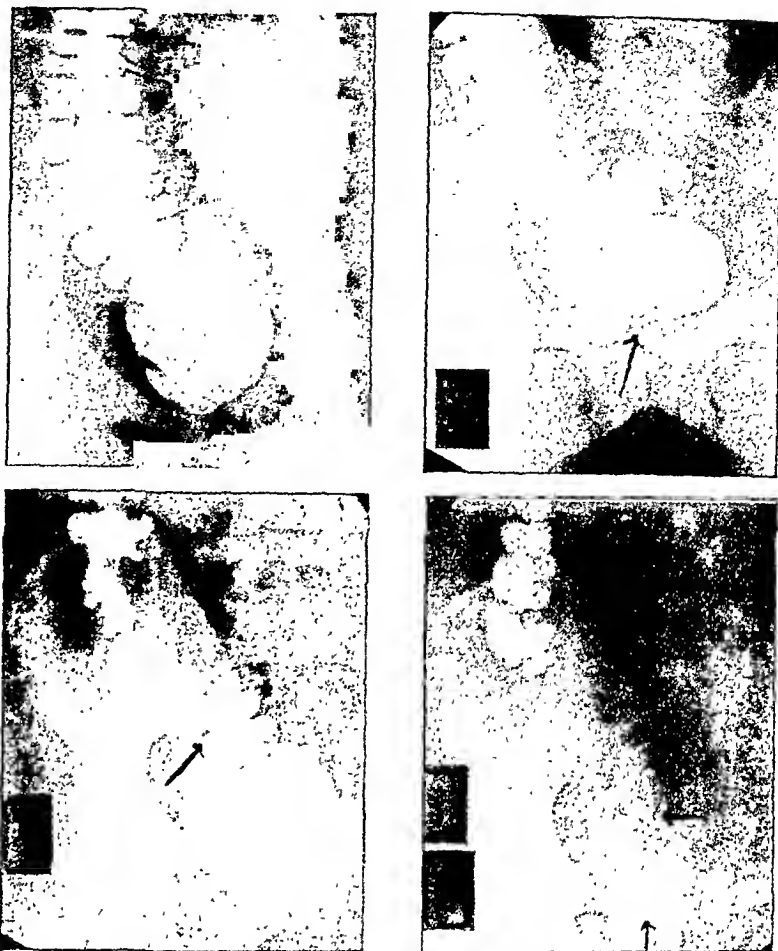


Fig. 3. Case 2. Atypical terminal ileitis.

Left upper. Nine hour film, taken in prone position. Terminal ileum and cecum huddled in one mass (arrow). No separate coils visualized.

Right upper. Nine hour film, taken in prone position. Upon the application of compression to the ilcoecal region, some of the terminal ileal loops are separately visualized as definitely dilated (arrow).

Left lower. Thirty-six hour film, taken in prone position. Note the marked kink and angulation of the cecum (arrow) and a certain irregularity in the outline of the cecum and ascending colon. Terminal ileum is still barium filled.

Right lower. Thirty-six hour film, taken in prone position. After cleaning enema a partial barium retention in the terminal ileum is still noticeable. Note the hazy, still definite separate visualization of some of the narrowed lumen of the terminal ileum (arrow).

at or around the ilcoecal juncture was demonstrated.

Compression applied to the right iliac fossa, with the patient in recumbent position, failed to separate the ilcal coils, and it was only occasionally possible to recognize some of the loops as markedly dilated, among the majority of the hazily visualized and pathologically narrowed ilcal coils.

The cecum showed certain irregularities of its haustration and there was a definite kink and angulation of the deformed, fixated, angulated and hyperdescendent cecum visible.

We made the diagnosis of *terminal ileitis with a superadded incomplete ob-*

*struction through adhesional bands around the ilcoecal juncture.*

The operation performed proved the presence of a terminal ileitis involving the last ten inches of that gut with a striking infiltration of the mesenteric glands. Adhesions as assumed were present in the form of isolated cord-like bands, constricting but not strangulating some of the loops of the terminal ileum. Some adhesions extended between the cecum and the wall of the lower abdomen.

The mesenteric fat tissue exuberantly invaded, nearly completely covered the entire portion of the involved terminal ileum. The latter, in an extension of about ten inches, looked heavy, red-

dened, darker, thickened, sausage-like, in sharp contrast to the adjoining normal ileum.

The heavily infiltrated glands coalesced into solid masses as one would find them in Hodgkins disease or in typhoid fever. The thickened and shortened mesentery fixated and nearly immobilized the terminal ileum.

Patient made an uneventful recovery and left the hospital two weeks after the operation, in good health.

Excerpts from the report of the pathologist (Dr. A. Shifrin):

"Gross specimen consists of a resected portion of ileum, measuring 25 cm. in length. . . . . At a distance of approximately 6 cm. of the proximal end the *valvulae conniventes* are distorted. The next 7 cm. are occupied by a lesion which is stellate in appearance, showing superficial and deep furrows in the mucosa. The latter is markedly edematous, thickened and indurated. It is not stony hard. The impression is that the mucosal surface is intact. The edges of this area are not indurated. There has apparently been stenosis at the site of stellate scarring. . . . . A second area with a very slight induration is found 9 cm. from the distal end. The mucosal surface is ulcerated, granular and slightly indurated. At a distance of 2½ cm. from the distal end there is a mucosal polyp which is delicate, reddened and measures 1 cm. by 0.3 cm. . . . .

*Microscopic study:*

. . . . . In places the mucosal epithelium is necrotic and ulcerated. The surface is in these places delimited by the exposed submucosal stroma. The latter is highly cellular, consisting mainly of plasma and roundcells. Polynuclear leukocytes are present but not in large number. There is edema. Numerous young fibroblasts and prominent reticulum cells are seen. This cellular infiltration in the main is well marked in the superficial portions of the mucosa, but it penetrates distinctly into the submucosa and even in places to the interstices of the muscularis. . . . . The submucosa shows aggregations of lymphocytes into follicles. Secondary lymph follicle-formation and reticulum cell hyperplasia is also observed. There is a striking hypertrophy of the smooth muscle tissue both in the mucosal and internal and external layers. Fibrosis is present but not marked. In places the cellular infiltration of the mucosal stroma has given a polypoid appearance to the mucosa.

It is of note to observe the absence of (1) caseous necrosis, (2) giant cell reaction of either the foreign body or Langhans' type of cells, (3) epithelioid tubercle formation, (4) mononuclear changes within the lymph follicles or hyperplastic inflammatory areas.

Diagnosis: subacute and chronic ulcerative regional ileitis."

## FOR PEPTIC ULCER A REVOLUTIONARY TREATMENT

### *Peptic Ulcer Becomes Symptom-Free on the* **LAROSTIDIN TREATMENT**

*One daily injection for about 24 days*

---

**Larostidin Ampuls, 5cc . . . Cartons of 6**  
**4 boxes constitute one complete treatment**

---

*After 5 days . . .* Pain usually disappears and does not recur. Nausea, vomiting, hyperacidity, and flatulence are relieved.

*After 10 days . . .* Normal diet well tolerated. Appetite improves. There is consequent gain in weight, general systemic improvement, and vastly improved mental outlook.

*After 24 days . . .* There is usually remission of all symptoms, viz.: food intolerance, gastric pain, and hyperacidity. Normal emptying time, normal peristalsis and absence of spasticity are evidenced.

DRS. VOLINI and McLAUGHLIN, *Medical Record*, April 17th, 1935 report: "The parenteral use of histidine monohydrochloride (larostidin, Roche) produces rapid clinical improvement in patients with gastroduodenal ulcer upon liberal diets and while ambulatory. Pain, vomiting, hypersecretion and retention quickly improve or disappear. Appetite and weight increase is noted."

BULMER, in reporting his results in 52 cases of peptic ulcer (*The Lancet*, Dec. 8, 1934) emphasized the fact that the Larostidin treatment is better than the older methods—alkalics, feedings, etc.—in bringing about complete subsidence of symptoms, and that these results are easily achieved with ambulatory management. Dr. Bulmer's paper was abstracted in the *Journal of the American Medical Association*, February 23, 1935, page 690.

---

**HOFFMANN-LA ROCHE, Inc., Nutley, New Jersey**

---

## The Practice « of Dietetics »

By L. H. Newburgh, M.D., Professor of Clinical Investigation, Medical School University of Michigan; and Frances Mackinnon, A.B., Dietitian, Diet Therapy Clinic, University Hospital, and Instructor, Dept. of Hygiene and Public Health, University of Michigan.

### Comments of reviewers—

"This is a very complete and scientific text and reference book on dietetics. The book will be of greatest value to the physician, the dietitian, and the medical student."

*The Forecast*

"In this book the place of dietetics and diet therapy in medical therapeutics is discussed in a manner that gives the reader a clear picture of its importance, and, at the same time, impresses him with the need for a sane point of view in its practice."

*Practical Home Economics*

"This book contains all the material necessary for the practice of dietetics. It is both didactic and practical. Dr. Newburgh writes as he practices; so direct, clear, and yet scientific that even the student or busy practitioner can understand."

*Long Island Medical Journal*

**\$4.00**

**The Macmillan Company**  
Publishers New York

## DISCUSSION

The first case shows a clear-cut, a typical instance of terminal ileitis. The history and the physical examination alone nearly assured the diagnosis, which has been completed by the characteristic X-ray findings and proven by surgery and the pathological examination of the resected specimen.

The second case, in contrast to this represents an *atypical appearance of terminal ileitis*. In this case, the history was by no means typical, it was probably more indicative of an obscure case of a milder sprue than of terminal ileitis. As we have seen, the physical examination proved likewise insufficient to substantiate the diagnosis. A careful X-ray study was necessary properly to diagnose the case. This showed a 36 hour retention in the terminal ileal coils. Motor power insufficiency in itself can not be considered pathognostic for regional ileitis. This can rather be encountered in any disease or condition causing stenosis or obstruction strictly distal from visualized gut.

The following may give an approximate idea what lesions might have come into question from the view point of a differential diagnosis: post-operative adhesions; appendicular and peri-appendicular abscesses; chronic appendicitis with adhesions, kink, angulation; right lower quadrant pathology: tubo-ovarian tumor, cyst, inflammation, abscess; tuberculosis: of the ileum, cecum and peritoneum; lues: gummata or glands; actinomycosis; carcinoma, primary or rarely metastatic; sarcoma; lymphosarcoma; benign tumors: lipoma, fibroma, myxoma; lymph gland enlargements: Hodgekins' disease, leukemia, or rarely: lymphogranulomatosis, reticulosis, foreign body granuloma; carcinoma, mucocoele or lymphoma of the appendix; congenital Jackson's membrane; Meckel's diverticular tumor, cyst, inflammation or strangulation through its rudimentary ligamentous band; localized idiopathic dilation of the ileum; multiple diverticula of the cecum with concretion; accumulated foreign bodies swallowed by the insane and at last terminal ileitis.

Our reasons for arriving at the diagnosis, as aforementioned, are the following:

We assumed the presence of adhesive bands for the following reasons: (1) the cecal angulation as evidenced on the film; (2) failure to

separate and individually clearly visualize the terminal ileal coils (which would point to the probability of the presence of adhesions among these loops); (3) the findings of adhesions during the previous appendectomy; (4) the well known tendency of terminal ileitis to develop postoperative adhesions.

If only such adhesions were present, then, the proximal loops would be all compensatorily dilated. The case not being so, we had to assume the presence of additional factors.

We assumed the presence of terminal ileitis on account of the following facts: (1) the process seemed to be strictly localized to the terminal ileum; (2) presence of adhesions, characteristic of this condition; (3) presence of both dilated and narrowed loops; the latter proving the intraluminal stenosis in the terminal ileum—a direct visualization of the narrowed lumen—loops of the former were pre-stenotic compensatory dilations. The visualization of the stenosed lumen, in the case of terminal ileitis, where the filling defect or the local hypermotility of the diseased gut (Stierlins' phenomenon) is the rule, would definitely point to the fact, that the motility of the diseased stenotic loops is impaired by some mechanical obstacle encountered at its distal edge. *Narrowed lumen proves intraluminal stenosis; its visualization points to the presence of some motor disturbance due to certain organic obstruction distal to the point*; (4) the visualization of the separated loops—whenver feasible—is not sharp because of the overlapping of the loops and the small barium content in the narrowed lumen, with a simultaneous heavy fibrotic thickening of the intestinal wall, and the presence of non-opaque adhesions; (5) absence of most of the typical symptoms of the diseases enumerated above; (6) relative frequency of the terminal ileitis; (7) data referring to the patient's age, to the protracted course of the disease, lack of cachexia, diarrhea, etc.

Though it seems to be fairly safe to assume that the terminal ileitis existed primarily, and the adhesions developed thereafter, the assumption of the reversed mechanism seems, however, not perfectly excluded. A congenital adhesion, like the remnants of a Meckel's diverticulum, may produce kink or strangulation, thereby circulatory and motor power disturbances, causing chronic irrita-



tions of the tissues in some of the intestinal loops. Like a chronic, un-specific granuloma may develop as a result of a chronic irritation due to the presence of a foreign body, or a specific granuloma may develop as a result of a chronic irritation brought on by bacterial or toxic agents as in tuberculosis, lues or actinomycosis, likewise, a primary adhesion with all its chronic irritative effect might occasionally produce a non-specific granuloma in the appearance of a non-specific terminal ileitis.

The chronic obstruction at the ileocecal juncture was not a complete one. In such instance the paralytic dilation of the hypertrophied small intestinal coils produces the well known picture of the multiple fluid levels with the gas bubbles thereon, and proximal thereto the small intestinal loops present the picture of the step-ladder or herring-bone appearance, on the X-ray films, which were all absent here.

The 36 hour delay as was observed in this case is unusual and atypical in terminal ileitis. Crohn, also Goldfarb, found the ileal coils on the 6 hour films usually empty. And that is the rule.

One should not lose sight of the fact that the content in the ileum is still liquid, and as a rule, it does not require much compensatory hypertrophy of the proximal loops to overcome the mechanical obstacle produced by the narrowed lumen in the terminal ileal coils. For that reason there may be no motor delay in the ileum as evidenced on the X-ray films. If there is any—as there was in our second case—there must be some additional factor responsible for this phenomenon, as was proven in this case by the adhesion around the ileocecal juncture.

Lastly, it should be recalled that an ileal retention rarely may find its explanation by the presence of either a pyloric stenosis, or a cecal regurgitation (Jordan) without an anatomical obstruction at the ileocecal region.

### CONCLUSIONS

Two cases of terminal ileitis are reported, a typical and an atypical one. In both cases pre-operative diagnosis was made.

In the atypical case a 36 hour delay was demonstrated in the terminal ileum, due to the complicating effect of adhesions around the ileocecal juncture.

Both cases recovered after a successful resection of the diseased area.

Failure to recognize the ailment early, is partly due to a faulty or unsatisfactory "routine" X-ray technic.

Early diagnosis is urged because a correct diagnosis followed by appropriate surgery offers an unusually good prognosis, with a permanent cure, while a failure to diagnose the case means chronic marasmus, with perhaps a fatal outcome.

### REFERENCES

1. Assmann, H.: *Klinische Roentgendagnostik der Inneren Krankheiten*. F. C. W. Vogel, Leipzig, 1924.
2. Carman, R. D.: *The Roentgen Diagnosis of Diseases of the Alimentary Canal*. W. B. Saunders Company, 1921.
3. Crohn, B. B.; Gluzburg, L., and Oppenheimer, G. D.: Regional Ileitis. *J. A. M. A.*, Oct. 15, 1932; Vol. 99; pp. 1323-1328.
4. Crohn, B. B.: The Broadening Conception of Regional Ileitis. *Amer. Jour. Digest. Dis. and Nutr.*, April, 1934.
5. Goldfarb, S. L.: The Roentgen Analysis of Lesions of the Small Intestines. *N. Y. St. Jour.*, June 1, 1934.
6. Jordan, A. C.: Chronic Intestinal Stasis. A Radiological Study. Oxford Medical Publications, 1926.
7. Kantor, J. L.: Regional (Terminal) Ileitis Its Roentgen Diagnosis. *J. A. M. A.*, Dec. 29, 1934; Vol. 103; p. 2016.
8. Meyer, H.: *Roentgendagnostik in der Chirurgie u. ihre Grenzgebiete*. J. Springer, Berlin, 1927.
9. Ritvo, M.: Roentgen Diagnosis of Lesions of the Jejunum and Ileum. *Amer. Jour. Roent. and Rad. Ther.*, Feb., 1930; Vol. XXIII, No. 2.
10. Soper, H. W.: The Roentgen Ray Diagnosis of Lesions of the Small Intestines. *Amer. Jour. Roent. and Rad. Ther.*, August, 1929; Vol. XXII, No. 2.
11. Stierlin, E., and Chaoul, H.: *Klinische Roentgendagnostik des Verdauungskansals*. J. Springer, Berlin, J. F. Bergman, Muenchen, 1928.

## TILDEN has Kept Faith with Physicians

## ELIXIR MALTOPEPSINE (Tilden)

IN conditions involving gastric and intestinal upsets, as a dietary aid, and as a palatable vehicle for prescriptions carrying Iodides, Salicylates, Nux Vomica, etc., physicians have prescribed MALTOPEPSINE (Tilden) for a good many years.

MALTOPEPSINE (Tilden) includes DIOSCOREIN, LACTIC ACID, DIAS-TASE and PEPSIN, with acidic and other ingredients, combined in a manner exclusive with Tilden.

An elegantly flavored fluid, MALTOPEPSINE (Tilden) may be used freely.

Physicians have established the prescription specialties of Tilden, one after another, by nearly a century of practical experience.



Correspondence from physicians is respectfully solicited.

## The Tilden Co.

The Oldest Pharmaceutical House  
in America

New Lebanon, N. Y.

St. Louis Mo

A. J. D. D. 9-35

## Insulin-Glucose Therapy in Coronary Thrombosis

By

GERALD J. KOHNE, M.D.  
DECATUR, INDIANA

THE following case is reported to emphasize the benefits of insulin-glucose treatment in coronary disease.

### CASE REPORT

The patient, 73 years old, male, has suffered for 8 years from sub-acute, combined degeneration of the spinal cord, during which time he has continually taken liver therapy in high dosage. For many years he has also had a severe pyuria due to a resistant chronic pyelonephritis.

His gastric analysis gave the following results: Material mucoid; total acid 5°, free HCl 0°; blood: none. At first he had a blood picture characteristic of pernicious anemia, but, since he has faithfully followed

the liver therapy, no further anemia of any kind has been present. Locomotion, gait and balance were partially interfered with by the cord changes but the latter never progressed to a complete paralysis. His blood pressure always has been low, 100 to 138/65 to 80. The radial arteries have been noticeably sclerosed for years; the aorta prominent in chest films, the heart normal in size and shape.

Early in October, 1934, while raking leaves from his lawn, he felt a sudden pain over the sternum, this was referred to the left shoulder. For several weeks he regarded this a "neuritis" and did nothing about it. The patient consulted me on Nov. 12, 1934; a diagnosis of coronary thrombosis seemed justifiable. No friction

Submitted July 1, 1935.

sound was heard but the electrocardiogram made at this time showed a definite "coronary" T wave in leads I and II (Fig. 1).

He was given 50 c.c. of 50 per cent glucose intravenously daily for 9 days, each dose containing 5 units of insulin. Quite marked general improvement occurred and there was considerable decrease in the amount of cardiac pain.

After keeping the patient in bed for 8 weeks, and contributing theobromine sodium salicylate Gr. V., after each meal, he appeared to be well again. At this time another electrocardiogram was made, and it will be noted that the T wave in lead II had become positive (Fig. 2). The man was permitted to be out of bed and gradually to resume his customary light duties. He has remained comfortable since.

#### SUMMARY

An instance is reported in which it is believed that the use of an insulin-glucose solution, given intravenously, greatly hastened improvement of an affection diagnosed (from history, physical examination and electrocardiographic studies) as coronary thrombosis.

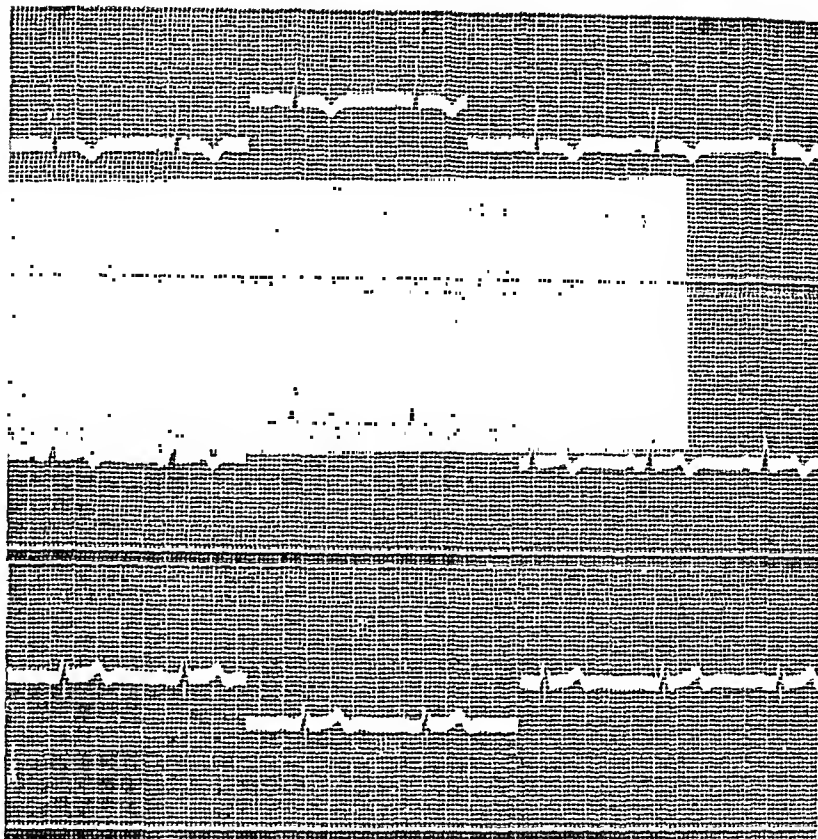


Fig. 1

## IN CHRONIC CHOLECYSTITIS . . . . .

not too far advanced, one measure that stimulates the secretion of bile, accomplishing relief in the majority of cases, is the application of

### Bile Salts Therapy \*



## TAUROCOL (TOROCOL)

### Bile Salts Tablets

have been used by the medical profession for nearly a quarter of a century. Samples and information on request.

\*Based on an article, "The Etiology and Treatment of Chronic Cholecystitis," by G. H. Cassity, M.D., Shreveport, La., appearing in the June, 1935, issue of Tri-State Medical Journal.

**The Paul Plessner Co.**

Detroit - - - - - Michigan

J. D. 9-35

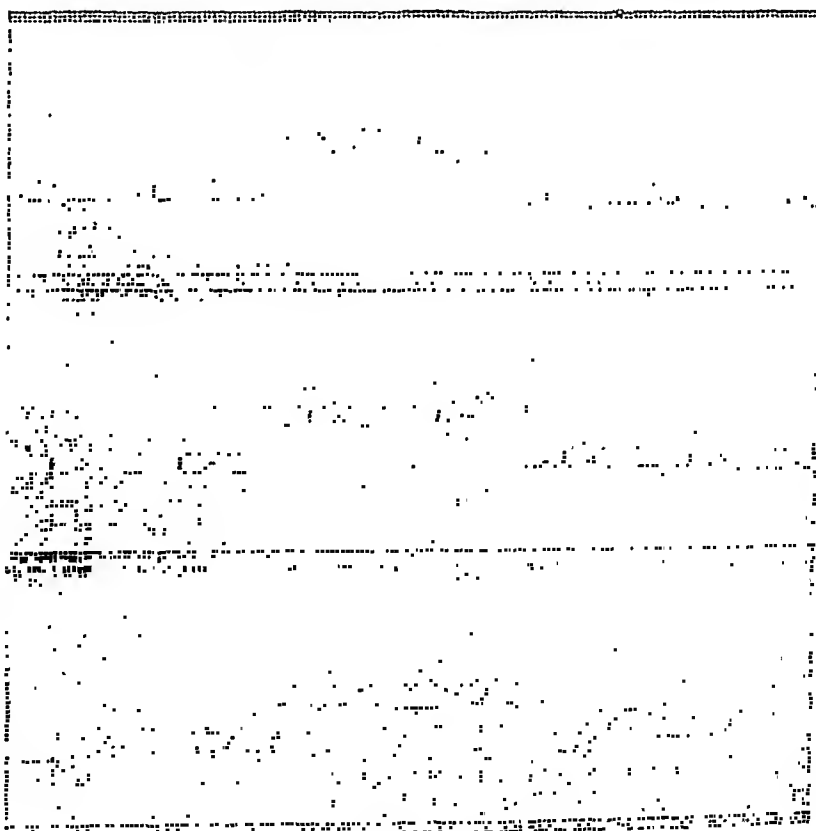


Fig. 2

## SECTION I—*Clinical Medicine: Diseases of Digestion*

### Acute Pancreatitis: a Clinical and Pathological Study, with Personal Observations

By

ALBERT LE SAGE, M.D., F.R.C.P. (Canada)\*

and

JEAN R. A. LE SAGE, B.A., M.D.†

MONTREAL, CANADA

**E**VEN at a casual glance, one cannot but be struck by the singular situation occupied by the pancreas in the abdomen. Indeed, this organ seems to covenant indissoluble alliances with the surrounding organs. It is connected with the general circulation by the blood vessels by which it is abundantly irrigated: the aorta, the pancreatic or duodenal artery, the splenic vessels and the portal system. It is encompassed by a vast network of lymphatic vessels with a centrepetal direction, and is accompanied by a mass of ganglions disseminated here and there, thus keeping it in close relations with the digestive tract, the appendix, the gall-bladder, and most of the organs located within the large cavity of the epiploön.

The head of the pancreas is set in the internal curvature of the duodenum, the second part of which receives the common duct with its orifice, the Vater ampulla provided with the sphincter of Oddi.

Its posterior surface rests on the spine against the third lumbar vertebrae, in the neighborhood of the solar plexus. It is a tubulo-alveolar gland with two secretions:

(a) *An external secretion* comprising ferments of which one, trypsin, has the action of breaking down the albumins whereas other ferments saponify fats such as lipase or, like amylase, convert the starches into maltose. Trypsin and lipase play the leading rôle in the question.

(b) *An internal secretion* originating from the Islets of Langerhans: insulin.

These elementary observations upon anatomy and physiology are useful to bear in mind.

#### ETIOLOGY

To simplify this *exposé*, let us admit that acute pancreatitis will be studied according to two forms: the septic, and the aseptic.

##### I. THE SEPTIC PANCREATITIS:

We shall deal briefly with the chapter of the septic form, as most authors point out the presence of well

known bacteria in more than half of the cases (those of peripancreatitis, or the pancreatitis with suppuration). All infectious diseases may give birth to acute pancreatitis: the organisms are carried by the blood vessels or the lymphatics, in other cases by the biliary tract, the duodenum, the neighboring organs, or may be the bacteria contained in the pancreas itself.

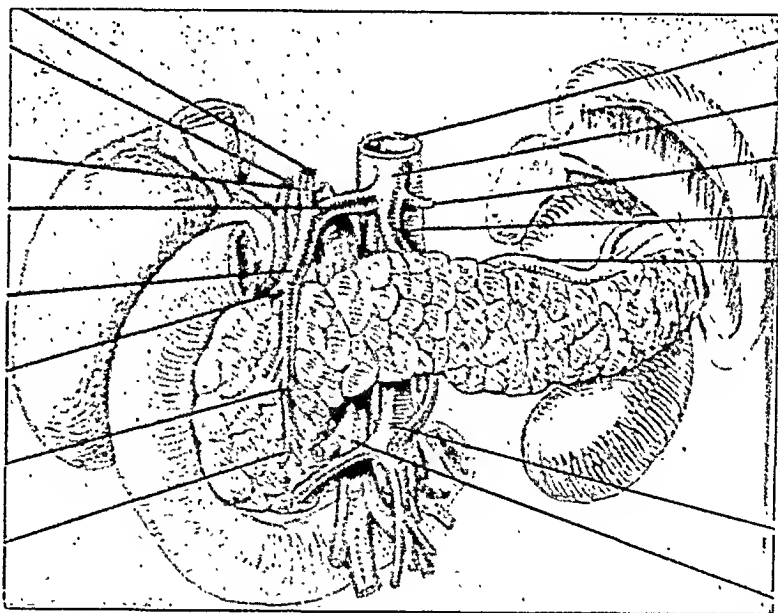


Fig. 1. Relations of the pancreas with the neighboring organs. The vascular system is easily recognized: the aorta in the center; above and at the left, the hepatic artery, the hepatic duct, the gastro-epiploic and pancreatico-duodenal arteries. At the bottom: the mesenteric artery, the duodenum, spleen and the kidneys. (Sobotta)

Let us mention some of the causes and ways of access to the pancreas:

1. The lymphatic system;
2. The blood stream;
3. The biliary tract, the duodenum, from which the septic secretions penetrate into the pancreatic ducts;

\*Professor of Clinical Medicine, University of Montreal.

†Chief Gastro-Enterologist, St. Luke's Hospital, Montreal.

Submitted July 29, 1935.

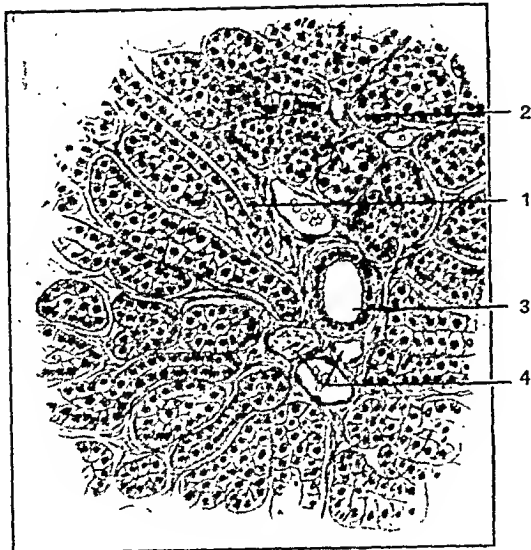


Fig. 2

4. Contamination due to a focal infection of the neighboring organs;
5. The increase of bacterial virulence (intracanalicular or intraglandular).

The arterial and canalicular theories are generally admitted by the majority of authors, but the theory of the lymphatic origin often is questioned. Some authors assert that the lymphatic system plays no rôle in the affections of the pancreas, whereas others, on the contrary, relying upon serious experimental research, claim to have succeeded in demonstrating the importance and frequency of this origin in relation with acute pancreatitis.

Both groups of oppositionists quote very illustrative experiences as a basis for their opinions.

Still, we believe in the rôle of the lymphatic "paths" of access of the infection in acute pancreatitis, because of the most intimate connections between the liver, the gallbladder and the duodenum, even the caecum, and the pancreas; moreover one should not entirely place reliance upon the experimental methods upon animals as applying to human pathology.

## II. THE ASEPTIC PANCREATITIS:

In order to facilitate their study, a subdivision is necessary:

### (A) The acute idiopathic pancreatitis:

1. The pancreatitis with oedema;
2. The pancreatitis with hemorrhage;
3. The gangrenous pancreatitis.

### (B) Acute pancreatitis with cancer;

### (C) Acute traumatic pancreatitis (?)

This division embraces most of the cases, with their various agents:

1. The mechanical origin (due to a stagnation in the bile ducts);
2. The chemical origin, due: (a) either to an over-

Fig. 2. Of the pancreas showing: 1, the alveoli; 2, the intra-lobular ducts; 3, the interlobular ducts; 4, the intra-lobular vessels and the nerves. (William Hinton, "Chronic Pancreatitis as a Clinical Entity," in Surgery, Gyn. & Obst.)

activity of the pancreatic ferments mixed with bile, or (b) to duodenal secretions or focal degeneration of the biliary and pancreatic ducts; (c) or due to autodigestion;

### 3. The degeneration of the pancreas:

- (a) Secondary to a malignant tumor;
- (b) Secondary to a vascular rupture, viz: due to an hemorrhage by stasis, arteritis, etc.
- (c) Secondary to a general intoxication;

### 4. Secondary to a traumatism (including the operative shock).

## PATHOGENESIS

According to what mechanism do these different forms of acute pancreatitis appear?

1. The mechanical origin: would be due either (A) to a stagnation in the biliary tract or (B) to the penetration of the duodenal secretion into the pancreatic ducts through an inadequacy of the ampulla of Vater, or by a retrograde path through the *ductus Santorini*, deprived of its sphincter.

(A) The stagnation of the bile in the ducts may take place either because of a gall-stone lying in the ampulla of Vater, or on account of an hyperacidity of the duodenal secretion with stasis producing a contracture of the sphincter of Oddi, which theory is well grounded on experimental and clinical facts in both cases. According to some authors, we are concerned with an abnormal elevation of the intracanalicular pressure followed by a flow of bile into the pancreas.

The pathogenesis of pancreatitis in the case of an obstruction caused by gall-stones in the ampulla of Vater, rests not so much on the intra-canalicular pressure as on the intermixing of the biliary and pancreatic secretions, giving rise to chemical transformations and to a true auto-digestion soon followed by an hemorrhage and necrosis of the organ. Normally the gland itself cannot be destroyed by the pancreatic ferments

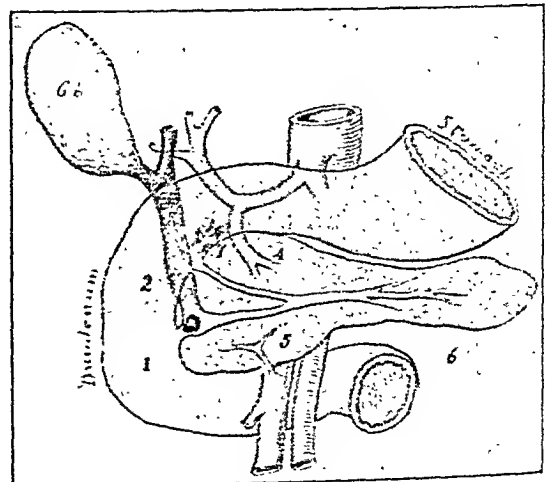


Fig. 3

Fig. 3. A descriptive schema showing several anatomical causes of Acute Pancreatitis: 1, the duodenal pathway to the Wirsung duct; 2, through the Santorini duct; 3, through the biliary ducts; 4, the arterial system; 5, infarct following a thrombosis of the portal vein; 6, a traumatism; 7, a duodenal ulcer infecting the pancreas through the lymphatic system. (Schmleden and Sebening)

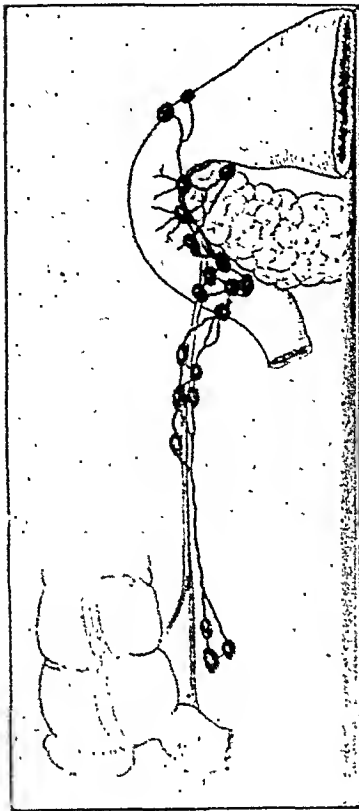


Fig. 4

as has been abundantly proven by experimental and even clinical research. It has been our privilege to observe an unusual case, where a tumor compressing the Wirsung duct in the very neighborhood of the ampulla of Vater had caused the accumulation of a large quantity of pure pancreatic secretion without the least trace of bile. The pancreas was atrophied, but no steatonecrosis or infarct was found.

Such are the following twin typical observations:

1. *Pancreatitis with oedema*.\*

Case 1. A woman, aged 50, complained of digestive troubles for the last three years with epigastric pains. During the last six weeks aggravation of the pain with vesperal fever (39° C) is observed. Pulse: 140. Upon examination a pain is found with a muscular "defense" in the right epigastric quadrant with an irradiation to the left hypochondrium. Leucocytosis: 11,800. later, 18,000, with 82.5% polynuclear cells.

A diagnosis of acute pancreatitis is made. Upon laparotomy, a yellowish liquid flows from the cavity. Gall-stones are found and the pancreas is enlarged, soft, bleeding copiously. Drainage. Recovery.

Case 2. *Pancreatitis with oedema* (Prof. A. LeSage, Montreal; unpublished): Mrs. V. T., aged 41, complains for two days about an epigastric pain radiating to the right and to the left hypochondria, the right radiation reaching the collar-bone, the shoulder and the back. Several anterior attacks. This time, the pain is so acute that she can hardly breathe. The maximum distress is localized in the epigastrium.

Upon examination, the Murphy sign is positive with phrenic irradiation, the gall-bladder being easy to delimit,

\*Irvin Abel. Am. Annals of Surg., Oct., 1926.

Fig. 4. Secondary infection of the head of the pancreas, following an injection of the ileocecal ganglions. (Braithwaith)

having the shape of a pear, in the epigastrium with a local resistance and a swelling. No stools were available; no gas passed for two days. The face is drawn. The pulse is slightly perceptible, slow at 55. A blood count shows: r.b.c.'s.: 2,000,934; w.b.c.'s.: 15,625; polys: 80%.

In the presence of this severe condition, of most acute pain, we diagnosed *hydropic cholecystitis*, probably with gall-stones followed by a pancreatitis, because of the pain, of its acuteness, its localization, its irradiation to the left as far as the back, and chiefly because of the severeness of the general condition, realizing in brief, a true solar plexus syndrome. Upon operation, the gall-bladder is found congested, much enlarged, containing calculi, and the pancreas exhibits oedema and congestion extending to the entire mesocolon. Drainage. Recovery. The patient, admitted on the 14th of January, 1928, left the hospital on the 17th of February.

This rare clinical observation comes in support of experimental researches published elsewhere.

(B) As much can be said about the spasm of the sphincter of Oddi. Many experimental researches of which those published by Brocq and Morel, from Paris, Flexner in the United States, and Archibald of Montreal, confirm this theory. The latter has succeeded in obtaining an acute pancreatitis with necrosis after injecting in the gall-bladder glyco-sodium taurocolates. Such is the consequence of stasis in the bile ducts that the intermixing of both pancreatic and biliary secretions, followed by a reactivation of trypsin, that finally is produced a brutal attack on the pancreatic gland; thence, an interlobular oedema, a congestion of the vessels, then a rupture, then hemorrhage and a necrosis.

The reactivated pancreatic ferments make irruption out of the gland and soon give rise, under the impulse of the activation of the lipase, to those well-known "candle-spots," known as *steato-necrosis*.

What are the substances activating these two ferments: *trypsin and lipase*?

According to the majority of authors who have repeated the experiments of Delezenne, the kinases (en-

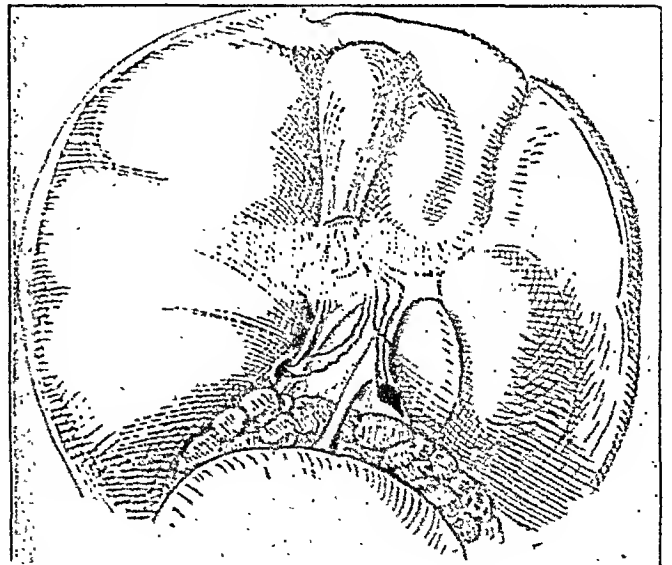


Fig. 5

Fig. 5. Relations between the lymphatic vessels of the gall-bladder and the head of the pancreas. (Bartels)

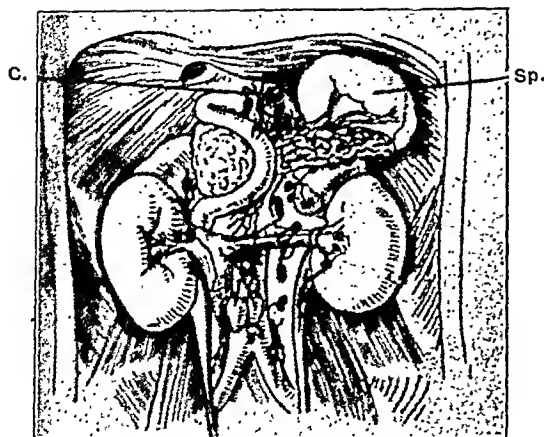


Fig. 6

terokinases or cytokinases) combined with the action of the calcium chloride of the blood, contribute to activate both these ferments, especially trypsin. The transmission of this activation would, in certain cases, give rise to an autoethonous kinase resulting in, (according to Delezenne), a phenomenon of auto-catalysis. In view of preventing this reactivation, this author advises an alkaline lavage of the stomach and the use of fluorate or oxalate of sodium.

However, let us add that a *period of digestion is indispensable before there occurs a pancreatitis with a hemorrhage*, such as an injection of bile into the pancreatic duct, this observation having been well shown in 1913 by Brocq and Morel (1). We shall establish further how clearly this fact is fully confirmed by clinical observations, the attack appearing two or three hours after a copious meal.

**Other causes:** Amongst other causes should be investigated the following ones: cholecystectomy with a compensating dilatation of the biliary ducts associated with a spasm of the sphincter of Oddi, intestinal parasites, of which a typical case, found upon autopsy, is further reported. On the other hand, gastric hyperacidity, leucocytosis, the nervous shock due to an irritation of the solar plexus, either following a compression, or following a painstaking operation, traumatism, contusions, may well be considered eventual causes of pancreatitis, notwithstanding conflicting experiences. Heart disease, prolonged vascular stasis with thrombophlebitis and infarcts are fairly frequent causes of pancreatitis with hemorrhage.

Age, sex, race, pregnancy, obesity, alcoholism, pyloro-duodenal ulcers, appendicitis, range amongst less frequent causes of this affection.

To conclude, perhaps the following order of frequency might be rightly adopted with respect the etiology of acute pancreatitis:

(a) The biliary tract diseases; (b) Duodenal ulcer and stasis; (c) Infarcts; (d) Intoxication; (e) Vascular stasis; (f) Intestinal occlusions; (g) Traumatism: contusion and surgical traumatism; (h) Parasites and all other causes.

Fig. 6. Relations of the lymphatic vessels of the pancreas in man with the territory of the lymphatic ganglions: C: Cardia; Sp.: Spleen. (Barteis), Arch. Anat. of Phys., 1904-06.

## SYMPTOMATOLOGY

1. *Pain* is the capital sign in acute pancreatitis. It is a sudden, violent, tenacious pain, resisting even morphine, reaching from the first its full acuteness. If persistent, it soon becomes intolerable, the location being usually epigastrie and supra-umbilical, but sometimes it is hardly possible to localize it with precision. It irradiates chiefly to the left hypochondrium and to the back, oftentimes to the right quadrant and towards the shoulder; in other cases towards the iliac fossa.

The time of pain usually is two or three hours after a copious meal or after abundant libations. The state of digestion plays an important rôle, the clinical and the experimental medicine being in full accord on this point.

2. *Vomiting* is contemporary with the pain, sometimes preceding it; frequently it is very abundant, tinged with blood, but rarely of the fecal type.

3. *The interruption of the bowel movement and the passage of flatus* are inconsistent; they are not so complete as in cases of intestinal occlusion, yielding to an hypertonic sodium chloride enema.

4. *The abdominal signs* are of great importance. Tympanitis with meteorism without local spasm or muscular resistance will be noticed although local tenderness and possible supra-umbilical or epigastrie contracture will be revealed chiefly in the pancreatitis

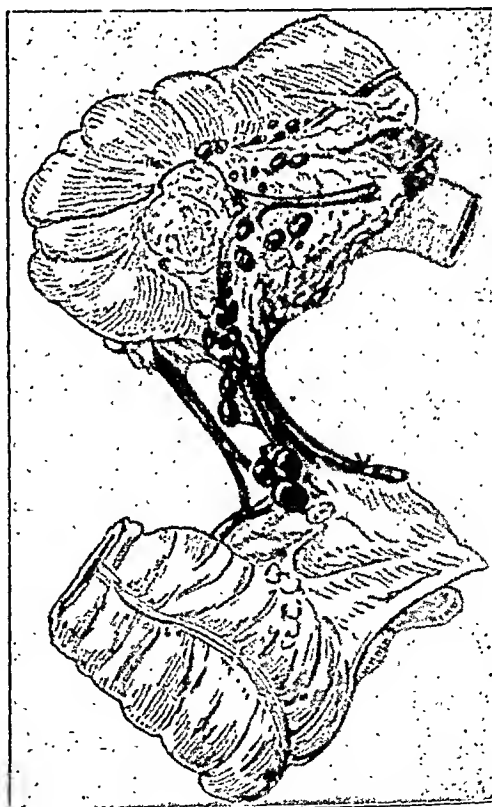


Fig. 7

Fig. 7. Post-mortem injection of the ileo-cecal ganglions and the flowing back of the liquid into the caecum and the head of the pancreas. (Braithwaith, Brit. Med. Journ., 1923)



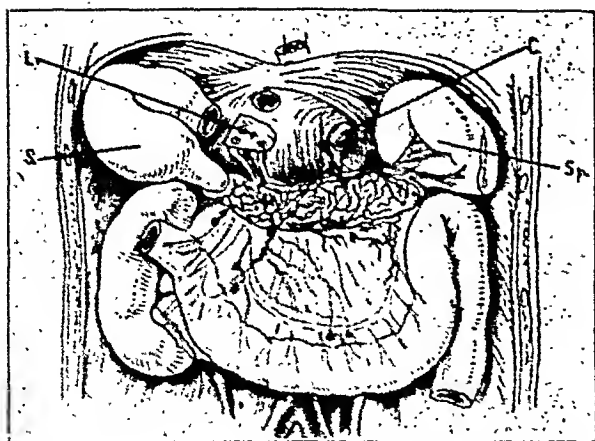


Fig. 8

Fig. 8. Further aspect of the relation between the lymphatic vessels of the pancreas in man and the territory of the lymphatic ganglions. (Bartels) S: Stomach; Sp. Spleen; C. Cardia; L. Pyloric ganglion.

with oedema. Pain may be induced upon a deep pressure in the pancreatico-duodenal region, whereas; in a few cases a tumefaction is felt.

Apart from the pain element, the investigator will be rewarded in studying the *history of the preceding attacks* ("crisis"), which will be discovered to have occurred in the majority of patients. Such are characterized by more or less frequent *indigestion coinciding with the eating of copious meals*, stopping abruptly, but resembling altogether the later crisis but the last one—that indicative of the acute pancreatitis—is far more severe than prior ones.

5. The *pulse* is feeble and quick, the temperature normal or subnormal, with an impressive "dissoia" with the pulse.

*Polypnea* is observed; *oliguria* is much pronounced with or without glycosuria.

6. *Glycosuria* is considered of great importance for prognosis. If it persists and increases, the prognosis is grave; if it decreases rapidly, the prognosis becomes rather favorable. Its interpretation lies in the fact that a total infiltration of the glandular parenchyma is prevalent when glycosuria is exhibited.

7. *Hyperglycemia* is closely related to glycosuria; a permanent hyperglycemia, "en plateau," during the first 24 hours usually is followed by death, a decreasing hyperglycemia offers a more favorable prognosis. In certain cases, it is advisable to perform, when possible, the tolerance type of blood sugar estimations in order to discover whether or not the pancreatitis associated with oedema is progressing towards a pancreatitis with hemorrhage. According to Bernhard, a test of glucose tolerance has reliable significance when performed as follows:

1. An initial estimation of the glycosuria and the glycemia;
2. Ingestion of 50 grms. of glucose in 200 c.c. of water;
3. A second estimation of glucose after 45 minutes;
4. A third measure of glycemia two hours later.

#### RESULTS:

1. A *constant hyperglycemia* is found (0. gr. 153 to 0. gr. 178 instead of 0. gr. 102) in acute pancreatitis without glycosuria;

2. A *glycemia* three times higher than normal (0. gr. 292 to 0. gr. 310 instead of 0. gr. 163) after 45 minutes;

3. The hyperglycemia-maximum is reached after

45 minutes in acute pancreatitis, whereas it appears two hours after the ingestion, with the diabetic and is characterized by a slowly rising curve.

In certain cases this method would allow us to follow the progress of an acute oedema of the pancreas towards a pancreatitis with hemorrhage.

8. *Radiography* at times has revealed the enlargement of the duodenum with compression of the bulb and a local stasis of the barium caused by pressure of the viscus by the enlarged pancreas.

9. *The test of diastasia* (1) is highly praised by the English and American schools. A thorough study of its value has also been pursued in France and in Rumania. Its presence in excess in the urine would indicate an undoubted acute pancreatitis. Normally, its index oscillates between 6 and 30 units. In acute pancreatitis, it often reaches 100, 200, and as far as 400 units. Great importance is being attached to this observation, and to the number of units as already quoted, with respect confirming a clinical diagnosis of acute pancreatitis. Still, a confusion exists concerning the mechanism of the phenomenon. Two different methods have been reported by us on this subject, a laboratory one, and an ambulatory one, to which we refer the reader for more details (1) (2).

10. *The blood count* has special characteristics: a drop in the number of the red blood corpuscles, quickly followed by a polyglobulia; a hyperleucocytosis ranging from 15,000 to 42,000 in certain cases, with an average of 25,000 in cases of pancreatitis with suppuration. We have personally observed two patients where the leucocytosis exceeded 15,000. Owing to an hypercholesterolemia, the blood-serum may resemble milk.

Other symptoms which have received well deserved consideration are:

1. The *Halstead* sign: that is, patches of cyanosis in the supra-umbilical region—a sort of local, hemorrhagic purpura;

2. The *Mayo-Robson* sign: a pain localized in the left, posterior, costo-lumbar region, corresponding to the location of the tail of the pancreas;

3. *Loewi's pupillary* sign or mydriasis by adrenalin: two drops of a 1 to 1000 solution are applied to

It takes about 40 minutes (including the 30 minutes' incubation) to perform the urinary diastase test, and, as no elaborate apparatus is required, the technique and time spent in its performance are both within the reasonable limits allowed by the preliminary preparations for operation on an acute abdominal condition.

In the present series, suitably graduated burettes for the saline and starch solution, and a pipette for dilutions were used in each case. However, in the absence of these facilities, it was found that a "diagnostic" reading could be obtained in a much simpler manner as follows. A one in 25 dilution of urine was prepared by adding one cubic centimetre of urine to 24 cubic centimetres of saline solution, one cubic centimetre and five cubic centimetres or ten cubic centimetre graduated syringes being used. One cubic centimetre of this diluted urine was now added to a small glass tube fitted with a stopper, for example, a Wassermann tube, and two cubic centimetres of 0.1% starch solution added. The tube was then placed in a vest pocket and the time noted. In about five minutes a small quantity was extracted and tested with a drop of iodine. If a blue colour resulted, the tube was "incubated" for a further five minutes and again tested, and so on until a test revealed a brown or reddish-brown colour, but not blue. This represented the end point, and meant that if attained within 30 minutes

there were at least  $\frac{1}{2} = 50$  units present. The test was thus often reduced by 15 or 20 minutes. Although a quantitative estimation was not made, a significant increase in urinary diastase was established.

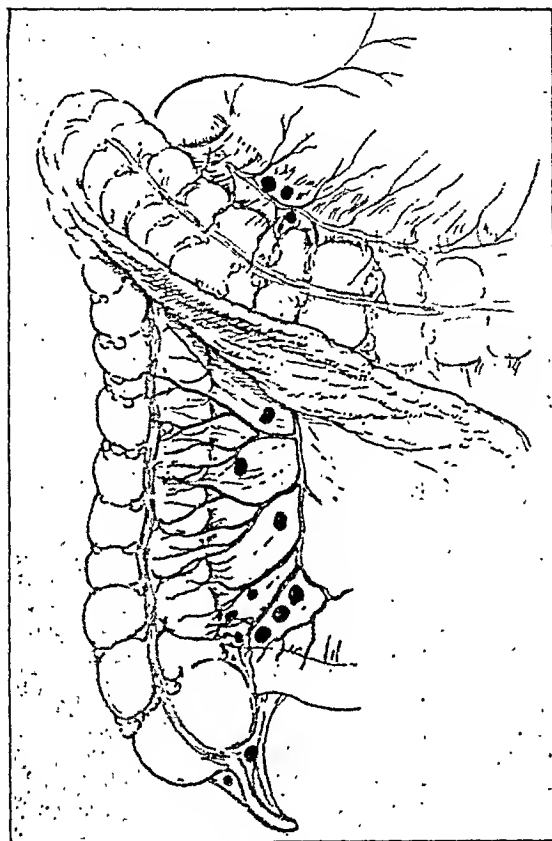


Fig. 9

Fig. 9. Congestion of the pyloric territory following an injection of the caecal and appendicular ganglions. (Brathwalth)

A living ascaride was found in the pancreatic duct, the head of the parasite was located in the tail of the pancreas.

**OBSERVATION II.** *Illustrating a retention of the pancreatic liquid in the Wirsung duct, with integrity of the pancreas* (Prof. A. LeSage and Pierre Masson). Mr. L., age 42, a house-painter, is admitted in the hospital on December 19th, 1933, for digestive troubles having started a month before, consisting of a tenacious *diarrhea* (10 stools per day, sometimes 20). A burning sensation felt at the epigastrium, accompanied by frequent regurgitations, belching and alimentary vomiting. Colicky pains are also complained of, located in the epigastrium. In 1930-31-32, the patient has complained of frequent indigestion associated with chills.

*General condition:* pallor, undernourishment, emaciation. The sensation of a foreign body or of a tumor complained of by the patient with a pain in the left hypochondrium towards the back. *Upon examination*, does not reveal more than a resistant epigastrium without a true muscular rigidity. The other regions show no tenderness whatever, but the pain complained of in the epigastrium, radiates to the left and to the back, whereas local pressure determines another pain definitely localized in the dorso-lumbar regions.

The examination of the stools showed the presence of neutral fats, of undigested muscular fibres without traces of starches. The Koch B. was not found. The blood-count, done repeatedly, showed a leucocytosis fluctuating from 10,000 to 18,000. No sugar in the urine specimens.

The character of the pain, the signs of an obvious pancreatic insufficiency with leucocytosis, had inclined us to the making of a diagnosis of a subacute lesion of the pancreas. The impression of a tumor made us think it was due to a cancerous lesion.

The autopsy revealed the presence of a tumor of non-cancerous nature, lying at a little distance from the ampulla of Vater, causing a compression of the Wirsung duct, which was in turn enormously dilated by large quantities of a pure pancreatic liquid imprisoned above the tumor. No bile was found in the liquid. The pancreas

the eye-conjunctiva and repeated after five minutes. The positiveness of the sign consists in a mydriasis half an hour later;

4. Other accessory signs will just be mentioned: the milky appearance of the blood-serum, jaundice, blood in the stools;

5. The *general condition* accompanying the signs especially mentioned is of outstanding significance. The constitutional condition is most impressive; usually it rapidly becomes adverse: a real condition of shock, with an anxious, drawn expression, a pale, livid complexion, a "pinched" nose, excavated eyes, cold perspiration, chilled and asphyxiated extremities; in brief, a state a severe collapse, although with it the patient keeps conscious..

#### PERSONAL OBSERVATIONS

**OBSERVATION I.** *Ascarides in the Wirsung duct.* A case concerning a man, aged 50, operated six hours after the outset of the disease, after a diagnosis of probable acute pancreatitis. A crucial pain in the epigastrium radiating towards the left hypochondrium and to the back, the patient being in a state of collapse. Upon laparotomy, bloody and serous liquid is found in the peritoneal cavity. The pancreas has a deep red color with hemorrhages and infarction. Death occurred 14 hours later. The autopsy revealed the lesions of hemorrhage and of steatonecrosis.

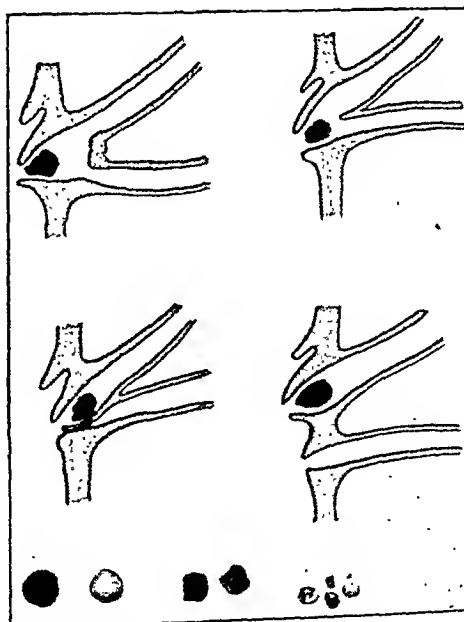


Fig. 10

Fig. 10. Presence of calculi in the ampulla of Vater, showing the anatomical types of calculi, their various localizations, the local obstruction and the eventual flowing back of bile from the biliary ducts or the duodenum into the pancreatic ducts. (Schmieden and Sebening)



Fig. 11

itself was more or less atrophied, with no traces of infarct or steatonecrosis. Neither were found any subacute lesions of the pancreas, but a plain stasis notwithstanding clean signs of an insufficiency had been verified in the stool analyses.

**OBSERVATION III.** (Prof. A. LeSage), *demonstrating some post-operative pancreatic accidents.* A man, age 52, is operated for a constant pain in the lower right abdominal quadrant and in the gall-bladder region. Upon laparotomy, lesions of perivisceritis between the duodenum and the gall-bladder, plus peri-cecal membranes are found. Three days after the operation, an epigastric pain appears, the acuteness of which becomes more and more pronounced. The medical treatment is followed by a slight improvement. The crisis soon re-appears, more severe, so that the patient dies during the night. The autopsy shows a pancreatitis with hemorrhage and necrosis.

We came to the conclusion that the painstaking surgical manipulations had caused a shock due to various draggings upon the solar plexus during the operation.

**OBSERVATION IV.** *Acute pancreatitis with hemorrhage* (From Gosset and Mondor). A female, 45, complaining of digestive trouble. The abdominal pains are unbearable during the night. Severe signs of a general intoxication, becoming aggravated every hour. The abdomen is swollen, tympanic, tender more than painful. Nothing is revealed by the palpation. No stools, no gas are passed. No contracture or "defense," but a resistance.

*Operation:* cholecystitis, lesions of steatonecrosis scattered over all the omentum; necrosis with hemorrhage. Hematoma located in the head of the pancreas, the former bulging forward into the stomach: a bloody serosity in the "arrière-cavité." An enormous calculus is in the gall-

Fig. 11. An aspect of the sub-meso-colic lesions of this patient. Shores of bullous oedema, surrounded by vascular colic arcades. Some elements (in clusters) are shown smaller, transparent, at the left of the mesenteric artery. (R. Couvelaire, "Acute Oedema of the Pancreas" a thesis. Paris, 1933, p. 85).

bladder. Temp. 38°; pulse 39°. Recovery after four months.

**OBSERVATION V.** *Cholecystitis with gallstones. Pancreatitis with secondary hemorrhage* (Prof. A. LeSage). A female, overweight, age 75, is admitted with a long standing history. For a year, she complained about repeated "indigestion" following large meals. The last spell was registered in December, 1933, when a sudden, very acute pain was felt in the epigastrium radiating around the waist and towards the right shoulder, necessitating an injection of morphine. Soon after appeared a jaundice with uncoloured stools. Temp. 103° F. Pulse: 110. A lull of 4 days, then there was a return of the accidents: a more acute pain in the epigastrium, with the same radiations and tenderness on palpation. There was local resistance, but the abdomen was not found retracted; there was no "defense musculaire." Bilious vomiting occurred. The general condition became more severe, and the patient was admitted in the hospital for an emergency operation.

*Operation:* a sero-bilious liquid was abundantly found in the peritoneal cavity with lesions of chronic cholecystitis and gallstones, the gall-bladder itself being hidden behind the network of adhesions. Owing to the age of the patient and the painstaking operation, a drain was placed and the operation quickly finished.

The following days, the disease takes a happy turn, but later the general condition again became aggravated. Blood leaked through the drain *following lavages*; the pulse was arrhythmic, and at times appeared a crisis of complete arrhythmia with cyanosis of the extremities and a deep alteration of the facial expression. The abdomen became more and more swollen. No stools or gas were passed notwithstanding the hypertonic salt enemas. The blood urea increased and the patient succumbed with all the signs of an internal hemorrhage.



Fig. 12

Fig. 12. Incision of the gastro-colic ligament, giving access to the pancreas and the cavity, where are produced and accumulate the serous and bloody liquids. (Schmieden and Sebening, in Surg. Gyn. and Obs., June, 1928, No. 6, p. 743)



Fig. 13

The autopsy was refused. There is no doubt, however, about the post-operative evolution of this case: a pancreatitis with necrosis and hemorrhage. The progress of the pancreatitis of biliary origin was carried on even after the operation, in accordance with several similar observations where proof had been possible. The autopsy is lacking, it is true, but it seems that the clinical signs are sufficient to teach us a lesson.

**OBSERVATION VI.** *Illustrating pancreatitis with suppuration. Cholecystitis with gall-stones and suppuration. Acute pancreatitis. Steatonecrosis* (Prof. A. LeSage). A female, age 53, was admitted to Notre-Dame hospital for a crisis consisting of paroxysmal pains alternating with long intervals of apparent good health.

Upon examination, the liver was found enlarged, the gallbladder painful, with phrenic radiations to the sub-clavicular regions and to the right shoulder. There was slight jaundice. Altho painful, the epigastrium was easily examined. It is elastic and only lightly swollen. There was constipation with uncolored stools. On the first days of Oct., 1933, the patient complained of a more severe spell than before. The pain, very acute, compelled her to be confined to bed. Morphine had but a temporary effect. The pain radiated definitely to the left and to the lumbar region. The tenderness was pronounced without a true contracture. The two lower abdominal quadrants are souple. Vomiting soon appears, first biliary, then bloody, without any effort. Temp. 102° F. Leucocytes: 25,000.

The clinical diagnosis was: Cholecystitis with gallstones—acute pancreatitis with suppuration. As the general condition was low, we endeavored to stimulate the patient in view of an impending operation.

Death occurred on the 12th of October, 1933.

**Autopsy:** (Prof. P. Masson) after a median incision of the abdomen, an adhesion extending from the anterior abdominal wall to the liver was detected, involving more precisely the gallbladder. Dissection revealed that the gall-

Fig. 13. Necrosis of the pancreas caused by the presence of an ascaris in the canal of Wirsung. (Schmieden and Sebening).

bladder, hidden behind a mass of local peritonitis, is drowned in yellow and green pus. From the larger abdominal cavity, 100 c.c. of dark liquid were recovered. The liver and gallbladder were drawn upwards, when suddenly a stream of very turbid liquid flowed out of the Winslow foramen. During this dissection, the gallbladder, most friable, was ruptured and gave a tablespoonful of pus, containing two dark green calculi, the size of a cherry-stone. From the gallbladder to the hepatic pedicle were found columns of thick pus; this process extended to all of the sub-peritoneal fat, the anterior region of pancreas, and the mesenteric pedicle. These yellowish frenums were covered with scattered white, opaque lesions of steatonecrosis. The liver was about the normal weight: 1,450 grams, very soft and congested. The histological examination showed cholangitic abscesses with innumerable bacterial colonies, in the sinusoids; also a variety of lesions of the parenchyma: anisocytosis, irregularity in the size of the nuclei, direct and mitotic divisions, cells showing a biliary retention (intra-cellular) and necrotic foci. Such are characteristics for intense toxi-infectious lesions.

The pancreas showed ancient lesions of the parenchyma consisting in the development of numerous microcysts containing an albuminous substance derived from the acini. It exhibits no suppuration, the latter being isolated from the fatty zones.

The fat tissue behind, chiefly pancreatic, covered purulent fistulas, the pus being entirely necrotic and surrounding or outlining nuclei of steatonecrosis.

**OBSERVATION VII.** *Cancer of the pancreas with glycosuria* (Prof. LeSage). Mrs. T., age 65, was admitted to Notre-Dame Hospital for persistent pains in the epigastrium radiating variously to the left or to the right, but appearing to have a maximum of acuteness in the dorso-lumbar regions, all of which have seemingly occurred formerly but have been aggravated since an automobile accident in August, 1934. During the collision, the patient was thrown to the back of the seat, and later showed marked distress in the pancreatico-duodenal quadrant.

Upon examination, the gallbladder was found painful and associated with phrenic and supra-clavicular radiations; another point was found in the epigastric region with radiations to the left hemithorax, a maximum point being detected on the two dorso-lumbar vertebrae. No other pain was recorded. B. W. negative. Spinal fluid: normal. Blood cholesterin: 1 gr. 84. Glycemia: 1 gr. 92. Urea: 0. gr. 74 and 0. gr. 35. The blood-count: Red cells: 4,300,000. White cells: 4,500. Hemoglobin: 75%.

Bleeding time: 3 minutes; coagulation time: 6 minutes;



Fig. 14. Pancreatitis with hemorrhage; a necrotic form involving the tail of the pancreas with a calculus in the ampulla of Vater. (Brocq, quoted by Mondor)

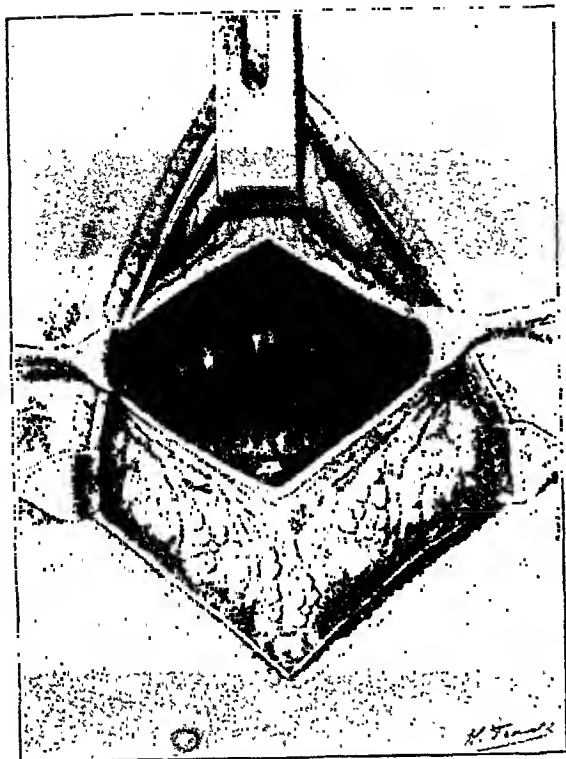


Fig. 15

Fig. 15. Acute hemorrhagic pancreatitis. Touches of fat-necrosis on the gastro-colic ligament, cut vertically.

Antecedents: no painful spells detected, no rhythm in the pain, no hematemesis or melena. Pronounced alcoholism is confessed, but luetic infection is denied.

The laboratory examinations suggested a partial confirmation of the previous diagnosis of chronic pancreatitis with probable cancer of the head of pancreas; this was strongly suggested to us by the patient's poor general condition, a very resistant pancreatico-duodenal region and a positive Murphy's sign (Chiray and Pavel). The total quantity of fats and meat fibres in the stool was high; the biliary pigments were reduced to traces. No parasites or occult blood were found. The Wassermann was negative in the blood and in the spinal fluid. Repeated duodenal intubations at fortnight intervals seemed to help the jaundice to retrogress and to produce a reappearance of the bile pigments in the stools; still, bile "B" did not appear once, whereas the examination of bile fractions, "A" and "C", showed very low concentration of pigments, biliary salts and cholesterol. Unexpectedly, two months after admission our patient was taken with lypothymia, severe epigastric pain, soon followed by very abundant melena. Death occurred a few hours later.

*Upon autopsy*, a large posterior duodenal ulcer was found; it had perforated into the pancreas, having ruptured the pancreatico-duodenal artery; also there was a chronic pancreatitis; a diffuse hepatic degeneration . . . but no cancer.

#### DIAGNOSIS

What diseases might be confused with acute pancreatitis? We propose to review the principal ones, in the order of their frequency, and keeping for the

in the urine, traces of albumin and urobilin; no acetone; no blood acidosis.

Pancreas: non-emulsified fats were found in the stools with numerous undigested meat fibres.

An X-ray examination showed the presence of calculi in the gall-bladder.

Twice glucose was found in good quantity in the urines.

On account of this complicated syndrome, we diagnosed: Cholelithiasis with a pancreatic insufficiency and subacute pancreatitis involving the body and the tail of the pancreas.

*Operation*: a dark bile is found in the gall-bladder with a small calculus. Cholecystostomy.

In the liver, 4 or 5 nodules the size of a chestnut are found, one of which was situated on the front edge of the liver, in the very neighborhoods of the anterior ligament of the liver. It was umbilicated, pinkish, rather hard.

In the pancreas, a mass as big as a chicken's egg was found in the head, behind the pylorus, which was intact but bulging forwards; there was a very indurated pancreas. Obviously, we had to do with an epithelioma with hepatic metastases. The patient eventually died from a neoplastic cachexia.

**OBSERVATION VIII.** For diagnostic purposes, to show that a latent duodenal ulcer may suddenly manifest itself like an acute pancreatitis (Dr. Jean LeSage, obs. 10,440). An old man, age 70, was admitted to the medical ward St. Luke's Hospital on July the 22nd, 1933, in a state of undernourishment, with a generalized but light jaundice. This jaundice had appeared very recently. Fifteen days ago there appeared vague digestive troubles: an epigastric sensation of heaviness, an indefinite pain in the two lower abdominal quadrants, belching, constipation, and suddenly, a syndrome of icterus with retention, pale stools, voluminous, very fatty. The appetite remained good.

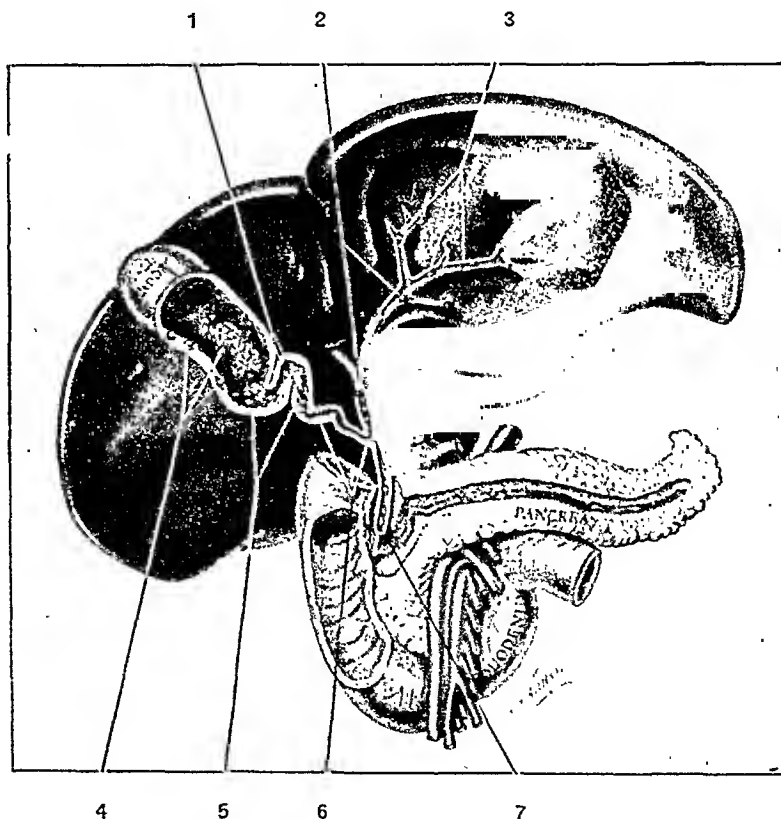


Fig. 16. 1, biliary calculus in the cystic duct; 2, calculi in the hepatic ducts; 3, intra-hepatic lithiasis; 4, dilated crypts filled with purulent secretion and calculi; 5, inflammatory thickening; 6, a frequent localization of cystic stenosis before its inosculation with the common duct; 7, calculi of the common duct above the ampulla of Vater.



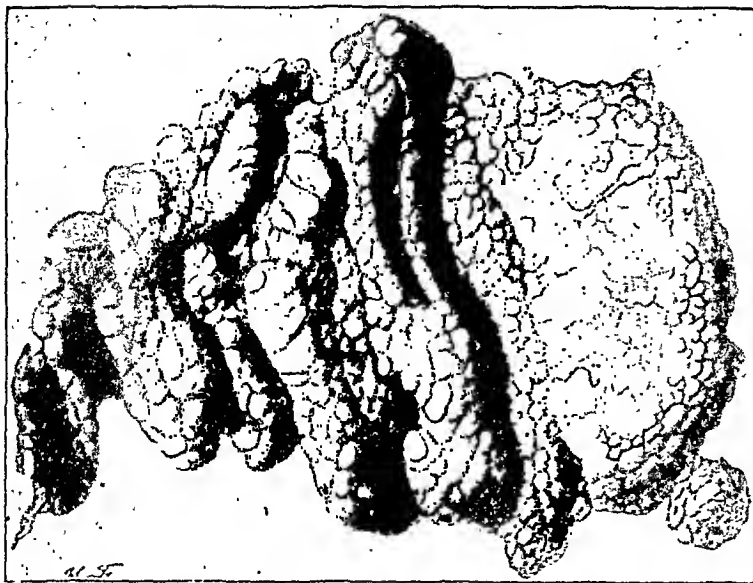


Fig. 17. Islands of fat-necrosis on the great omentum (Mondor).

last those requiring the more delicate differential diagnosis.

1. *Acute gastritis*, which is often preceded by certain sympathetic or motor troubles, such as a tenacious cephalalgia, palpitation, fainting, a sensation of gastric or intestinal distress, a respiratory embarrassment or an epigastric distention. In this affection, uneasiness, more than pain, is complained about, the uneasiness persisting several hours and even days. Alkaline or bilious vomiting terminates the attack, whereas, in acute pancreatitis, the attack reaches at once its "acme." No "period of incubation" is noticeable as in the acute gastritis.

2. *The gastric crisis of tabes* are occasionally confused with acute pancreatitis, as they often burst out of a sudden, with a transfixiating pain, unyielding to morphine, followed by acid or even bloody vomiting; but such a spell will last a few hours, then often disappearing abruptly after an intravenous injection of atropine. A few signs of organicity may lead to the diagnosis, such as a positive Argyll-Robertson pupil, the absence of the patellar reflex, a positive Rhomberg, etc.

3. *A gastric or duodenal ulcer* might suggest the possibility of a pancreatitis. In favor of an ulcer however we have the periodic pains at regular hours, two or three hours after each meal and the fact that they are relieved by food or alkalis. No abdominal distention is found. In the case of a perforation, one can be guided by the classical diagnostic tripod: (a) A sudden, atrocious pain; (b) a parietal resistance localized to the supra-umbilical region accompanied by epigastric tympanism; (c) a few *dyspeptic antecedents*. An error in diagnosis will not influence the final decision which is one of surgical intervention.

4. *Acute appendicitis* is associated with a number of well proven clues: a dull pain in the lower, right, abdominal quadrant, often hidden behind the mask of an indigestion, accompanied by vomiting, constipation, or gas occlusion, muscular resistance, "ventre de bois." No pain irradiation except possibly to the corresponding leg. Usually, the pain is relieved by morphine.

Collapse and cyanosis occur in the case of a generalized peritonitis only. Hyperleucocytosis. Here also, no hesitation should hold back an emergency operation.

5. *The torsions or twistings* of the bowels are accompanied by paroxysmic pains, interrupted by short "lulls." The gas and stool occlusions, the meteorism, should rapidly decide on surgical intervention.

Moreover, in such cases we are now approaching the disconcerting grounds of intestinal obstruction, where invagination, "volvulus," stenosis with frenum and intestinal infarct are to be found closely associated.

The diagnosis rests upon the appreciation of the symptoms, seldom easy to ascertain, the doubt about which soon disappear however after an early operation.

6. Let us briefly mention: the *intestinal infarct*, with or without mesenteric thrombosis, which is revealed more

by the signs of an intestinal hemorrhage than by those of a shock;

The *iliac agony*, with the signs of an obstruction of the small intestine, early vomiting soon becoming fecal and associated with oliguria;

The *acute gastro-duodenal dilatation* recognizable by the profuse and easy vomiting, the filiform pulse, a total atony of the intestine and hiccoughs. It is a dramatic accident, sometimes post-operative; the prognosis always is severe.

7. Pancreatitis could hardly be confused with a *nephritic colicky pain*, as in this affection the pain is lumbar and the irradiations tend towards the inguinal regions, the thigh or the genital organs.

8. To the *hepatic colicky like pain* should be given a greater significance because of its frequency, its dorsal and clavicular irradiations. No shock nor collapse here is to be found, whereas the previous history of the case will bring forth several clues.

On the other hand, the hepatic colic like pain often is associated with lesions of acute pancreatitis. It is undoubtedly in such cases that the association of the symptoms will incline the physician to hold in suspense a final diagnosis of pancreatitis, as he is already hypnotised by the characters of the colicky pain.

Would it be superfluous to suggest that the following simple axiom be borne in mind to stigmatize this important chapter of medical pathology: the decision to carry through the diagnosis of an acute pancreatitis will most of the time depend upon the fact that one has thought of it and has acted promptly, keeping uninfluenced by a network of contradictory symptoms, which have made so true the well-known motto that "Il y a des malades plutôt que des maladies."

#### SUMMARY

This report might be briefly resumed in the following propositions:

1. *Acute pancreatitis* is more frequent than is usually believed, as it is often hidden behind the mask of the indigestions.



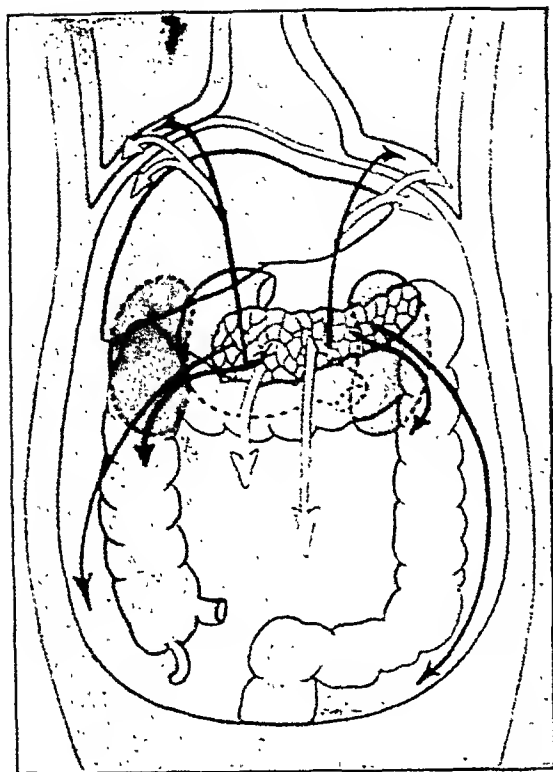


Fig. 18

2. Amongst the causes, let us enumerate in order of frequency:

- a. Gall-bladder and biliary duct diseases;
- b. Duodenal ulcer, and duodenal stasis;

Fig. 18. How the pus and blood issuing from the pancreas reaches the peritoneal cavity (Schmieden and Sebening).

- c. Infections;
- d. Intoxications;
- e. A vascular stasis;
- f. Intestinal obstruction;
- g. Traumatism: contusions and surgical trauma;
- h. Parasites and other causes.

3. *The pancreatic syndrome* progresses, as a rule, in the following manner; oedema, hemorrhage, necrosis, suppuration, the former relapsing, but spontaneously curable, although progressing towards the more severe form.

4. *The clinical symptoms* of difficult appreciation in the majority of cases, reach a higher acuteness in the oedematous form, which is curable, than in any others, often fatal. The pain and general condition must be our best guides in the estimation of the disease.

5. *The diagnosis* must be rapidly decided upon, because the emergency operation becomes a law, especially if a thorough investigation and a brief analysis of the various diseases or syndromes involving the organs situated in the vast hepato-gastro-pancreatico-duodenal territory has been carried through.

6. *Acute pancreatitis* should be more frequently thought of, the evolution being a deceptive and insidious one, and the prognosis, oftentimes fatal.

#### REFERENCES\*

- Archibald, E.: Acute oedema of Pancreas; clinical and experimental study. *Ann. Surg.*, 1929, p. 803.
- A general consideration of Pancreatitis. *Int. Clin.*, 1918.
- Archibald, W. A.: The experimental production of pancreatitis in animals as the result of the resistance of the common duct sphincter. *S., G., and O.*, June, 1929.
- Further data concerning the experimental production of Pancreatitis. *Ann. Surg.*, Oct., 1921.
- A new factor in the causation of Pancreatitis. Seventeenth Int. Congress of Med., London, Aug., 1913.
- Archibald, W. A., and Kaufman, M.: Surgical diseases of the Pancreas. *Practice of Surgery*, 1929.
- Brocq, P.: Pancréatite aiguë hémorragique. *J. de Chir.*, 1925, p. 7.
- Pancréatites aiguës médicales. *Prat. Méd. fr.*, 1926, No. 7.
- Pancréatites aiguës chirurgicales. Paris, Masson et Cie, 1926.
- Brocq, P., and Binet, L.: Pathogénie de la pancréatite aiguë hémorragique. *Presse Méd.*, 1923, p. 219.
- Chiray, Pavel et Le Sage, J.: Diabète et Cholécystite. *Presse Méd.*, Sept., 1932.
- Couvelère, R.: Oedèmes aigus du pancréas; étude clinique et expérimentale. *Thèse de Paris*, 1933.
- Le diagnostic chirurgical (Laparotomie exploratrice) au cours de la phase initiale de la pancréatite aiguë hémorragique. Paris, 1932.
- Flexner: *J. Exper. Med.*, 1906, p. 8.
- Le Sage, Albert: Pancréatites chroniques et angio-cholécystites encléusées. (Soc. Med. de Montréal, séance de mai, 1909. *Union Méd. du Can.*, Juillet, 1909, p. 373.
- Infection des voies biliaires. *Rapport général au XIème Congrès des Médecins de langue française de l'Amérique du Nord*, Juillet, 1905, à Québec.
- Le Sage, Albert: Pancréatites: Insuffisance des deux sécrétions; les petits signes. *Bulletin de la Société Médicale de Québec*, Fév., 1929.
- Le Sage, Albert: "Les Syndromes des Pancréatites Aigues." *Rapport Général Au XXIII Congrès des Médecins de France*, A Québec Août, 1934.
- Love, R. J. M.: Acute pancreatitis; clinical features and treatment. *Lancet*, 1926, p. 1252.
- Treatment of acute pancreatitis. Hunterian lecture. *Lancet*, 1929, p. 375.
- McWhorter, G. L.: Preventive surgery of pancreas and bile ducts. *Ill. Med. J.*, 1925, p. 128.
- Cysts of the Pancreas. *Arch. Surg.*, 1925, p. 11.
- The surgical significance of the common duct sphincter. *S., G., and O.*, 1921, p. 32.
- Report of 64 cases of acute pancreatitis. *Arch. Surg.*, 1932, p. 958.
- Non-perforative appendicitis followed by peritonitis of abscess. *Ill. Med. J.*, Aug., 1921.
- Mondor, H.: Pancréatite aiguë hémorragique avec infarctus mésentérique supérieur secondaire à une hypertrophie du cœur. *Bull. méd. Suppl.*, 1933.
- Monod, R. C.: Diagnostic des pancréatites aiguës. *Bull. méd. Suppl.*, 1933.
- Mushin, M.: Urinary diastase in acute pancreatitis. *Austral. and N. Zeal. J. Surg.*, 1932, p. 133.
- Quick, B.: Acute pancreatitis. *Austral. and New-Zeal. J. Surg.*, 1932, p. 115.
- Senn, N.: The surgery of the Pancreas. *J. A. M. A.*, 1886.
- Schmieden, V.: Acute pancreatitis. *Med. Klin.*, 1927, p. 419, and Acute pancreatitis. *Deutsche med. Wochenschr.*, 1927, p. 360.
- Schmieden, V., and Sebening, W.: Surgery of pancreas with especial consideration of acute pancreatic necrosis. *Arch. of Klin. Chir.*, 1927, p. 319, and *S., G., and O.*, 1928, p. 735.
- Schmieden, V., and Sebening, W.: Surgery of pancreas with special reference to necrosis. *Rev. med. de Hambourg*, 1928, p. 5.
- Wohlgemuth, J.: Diagnosis of acute pancreatic necrosis by determination of diastase content of urine. *Klin. Wochenschr.*, 1929, p. 1253.
- Zoepfel: Deux observations de pancréatite oedémateuse. Berlin, 1922.

\*We only publish a brief part of the bibliography published in our report to which we refer.

# Bacteriological Observations in Disease of the Biliary Tract

## A Comparison of Operative Findings with those of Non-Surgical Drainage of the Biliary Tract in 104 Cases\*

By

EILIF C. HANSSSEN, M.D.†

and

ANTONY YUREVICH, M.D.

NEW YORK CITY, NEW YORK

THE importance of obtaining reliable evidence with regard to infection of the biliary tract long has been recognized. Various attempts have been made to evaluate the rôle played by infection in disease of the biliary tract by bacteriological examination of specimens removed at operation.

Rosenow (1) in 1916, reported fifty-five per cent of positive cultures of specimens of "operative" bile. He also reported cultures of the cystic duct lymph nodes in which streptococci were obtained in sixty-three per cent; other organisms obtained were *B. coli*, *B. welchii*, *B. proteus*, and diphtheroids. There was a relatively high percentage of mixed infections in both series of cultures. More recent investigators, Drennen, Blalock, Johnson, Kelly, Judd, Mentzer and Parkhill, Illingworth, Wilkie, Branch, Williams and McLachlan, and Gordon, Taylor and Whitby, on the contrary have reported a predominance of cultures showing a single variety of organism. Drennen (2) in 1922, reported cultures of the fluid contents of operated gall-bladders in 100 cases, and found nineteen per cent to be positive, the predominating organisms being *B. coli* and staphylococci. Eighty-one per cent of the bile cultures were reported as sterile. Mixed cultures occurred in not more than five per cent of these cases.

Blalock (3), in 1924, reported 58% positive cultures in a series of 270 specimens of operative bile from the gall-bladder with 6% mixed cultures. *B. coli*, staphylococcus, and *B. typhosus* were the predominating organisms.

Johnson (4) of the Cleveland Clinic, in 1925, made a bacteriological study of the operative bile in 100 cases. He found it to be infected in thirty-two per cent of these. When infection was present a single variety of organism, usually staphylococcus or *B. coli* was found. Kelly (5), in 1926, reported the results of culture of the wall of the gall-bladder in 240 cases from the Clinic of Dr. Deaver. Forty-seven per cent of these cultures were positive. Practically all the infected cases showed a single variety of organism of which the staphylococcus, *B. coli*, and *B. typhosus* predominated. Judd, Mentzer, and Parkhill (6) in 1927, studied 200 operated cases and found the bile infected in fifteen per cent. The majority of cultures again

showed a single variety of organism of which the streptococcus and *B. coli* were most frequent. Among the organisms found by these investigators in the gall-bladder wall and in gall stones were the staphylococcus, streptococcus, *B. coli*, *B. welchii*, and *B. proteus*.

Illingworth (7), in 1927, reported bacteriological findings in cultures of the wall of the gall-bladder in 100 cases. The cultures were positive in 62% of cases, mixed cultures occurring in only 5%. The same investigators found pure cultures of *B. coli*, staphylococcus and streptococcus in 30% of 23 cases in which calculi were studied bacteriologically.

In 1927, A. L. Wilkie (8) of Montreal, working in Professor D. T. D. Wilkie's Clinic in Edinburgh, reported bacteriological studies of specimens of fluid contents and wall of the gall-bladder, and of the cystic duct lymph glands. He found that bile inhibited the growth of the streptococcus, and that for the same reason cultures of the entire wall of the gall-bladder frequently proved sterile, whereas those of the submucosa showed streptococci. Inasmuch as culturing the submucous coat was unreliable, because so frequently the specimen was contaminated, at Professor Wilkie's suggestion, cultures from the cystic duct lymph glands in all cases of cholecystitis were made. He found an astonishingly high percentage of positive cultures in the cystic duct lymph glands. In 43 out of 50 cases (86%) the cystic duct lymph gland yielded streptococcus in pure culture, one case showed *B. coli*, one case *B. welchii*, and only five cases proved sterile.

Nickel and Judd (9), of the Mayo Clinic, state that contrary to the experience of Wilkie, in their experience, bile did not inhibit the growth of organisms unless present in rather large amounts. Their series of 300 specimens of the wall of the gall-bladder yielded positive cultures in 50% of cases, the predominating organisms being streptococcus, a bacillus, and a staphylococcus.

Branch (10), in 1929, reported bacteriological studies in 210 cases of cholecystitis, culturing specimens of fluid contents, and wall of the gall-bladder, and gall stones. He found the bile infected in 19%, the wall in 25%, and the calculi in 29%. Mixed cultures occurred in 5% of cases. *B. coli*, staphylococcus, and streptococcus predominated.

Gordon-Taylor and Whitby (11), in 1930, reported 28% positive cultures in 50 cases in which cultural studies were made of gall stones at operation. All were pure cultures. These investigators also found

\*From the Departments of Medicine and Surgery of the New York Post-Graduate Hospital.

†Assistant Surgeon.  
We wish to record our indebtedness to Dr. R. Franklin Carter, Dr. J. Russell Twiss, and Dr. Adele Sheplar through whose kindness the data used by us in this paper were made available. We are also grateful to Dr. Carl H. Greene for his valuable assistance.  
Submitted July 8, 1935.

positive cultures in the wall of the gall-bladder in 82%, and in the fluid contents of the gall-bladder in 32% of cases. By making anaerobic cultures as well as aerobic ones they found in addition to the usual predominating *B. coli* and staphylococcus, a high incidence of *B. welchii*.

Williams and McLachlan (12), in the same year, performed similar studies. They found the wall of the gall-bladder infected in 51% of 84 cases. The fluid contents of the gall-bladder yielded 47% positive cultures in 81 cases. Pure cultures occurred in all but 7% of cases. Positive cultures were obtained in 56% of 43 cystic duct lymph nodes studied. The usual organisms found were the staphylococcus, *B. coli*, and streptococcus.

Whipple (13), in 1931, reported bacteriological studies in 178 cases of disease of the biliary tract. The various tissues studied yielded positive cultures in 60% of the cases. *B. coli*, staphylococcus, and streptococcus predominated. *B. typhosus* occurred in 4% of cases, and *B. welchii* in 3%.

In 1932, Magner and Hutcheson (14) reported positive cultures in 89% of specimens of the wall of the gall-bladder in 200 operative cases, and 33% positive cultures in 106 cases in which cultures were made of the fluid contents of the gall-bladder. The organisms which occurred most frequently were *B. coli*, streptococcus and staphylococcus.

In Rehfuess's (15) recent composite review of 2162 cases of cholecystitis studied bacteriologically following cholecystectomy, 45% of the cases yielded positive cultures from the wall of the gall-bladder, 29% from the fluid contents of the gall-bladder.

The wide variation in percentages reported by the various investigators may be explained by the fact that some series included more acute cases than others. Branch (10) found that in chronic cholecystitis the gall-bladder is infected in approximately 12% of the cases, whereas in acute cholecystitis the percentage rose to 75%. Nickel and Judd's (9) findings in this regard are in close agreement with those of Branch. Another factor may be the lack of uniformity in culture methods.

#### AUTHORS' INVESTIGATIONS

The present study, which was made in The Clinic for Diseases of the Liver and Biliary Tract of the New York Post-Graduate Hospital, includes 104 cases of chronic cholecystitis studied at operation. In these cases, cultures were made of the wall of the gall-bladder and fluid contents of the gall-bladder and of the cystic duct lymph node, and gall stones when present.

Bacteriological studies of the specimens removed at operation were made in the Department of Bacteriology under the direction of Dr. Adele Sheplar.

The methods used were as follows (16):

Specimens for culture were placed into previously labeled sterile test tubes by the surgeon at the time of operation. Gloves and sterile instruments were used in handling the specimens but no washing or searing of the gall-bladder wall or calculi was done. The test tubes were then immediately transferred to the bacteriologist who added the culture media. The gall-bladder was cultured in dextrose broth, the bile in dextrose broth and on blood agar plates as well. Aerobic cultures were the only ones made. Cultures were examined at the end of twenty-four hours. If no growth was present, they were reincubated and observed daily for four days. If a growth was present, the colonies were identified. Coliform colonies were

seeded in carbohydrate media in fermentation tubes for production of acid, gas, and determination of type. From the dextrose broth culture, Gram's stain was done on a film preparation. If streptococci were present, subcultures were made on blood agar plates to determine the action on blood and to complete the identification.

For the detection of typhoid bacilli, Endo medium was used as well as a tube of dextrose broth. If no typical colonies of *B. typhosus* were present, subcultures from the twenty-four hour broth cultures were made on Endo medium.

The results of the operative findings in the 104 operated patients as well as a comparison with the data reported by previous investigators are shown in the accompanying Tables I-V.

In our series all specimens were sterile in 67.3 per cent of cases (Table I). Positive cultures were ob-

TABLE I  
Frequency of Infection in Operative Specimens

|                       | No. of Cultures Taken | No. of Positive Cultures | Positive Cultures-Per cent of Cultures Taken | Incidence of Infection-Per cent of Total No. of Positive Cultures |
|-----------------------|-----------------------|--------------------------|----------------------------------------------|-------------------------------------------------------------------|
| Total No. of Cases    | 104                   |                          | 100                                          |                                                                   |
| No. of Cases Sterile  | 70                    |                          | 67.3                                         |                                                                   |
| No. of Cases Infected | 34                    |                          | 32.7                                         | 100                                                               |
| Gall-Bladder Wall     | 98                    | 29                       | 29.6                                         | 85.2                                                              |
| Gall-Bladder Bile     | 100                   | 20                       | 20                                           | 59                                                                |
| Cystic Duct Node      | 58                    | 13                       | 22.4                                         | 38                                                                |
| Gall Stones           | 26                    | 8                        | 30.7                                         | 24                                                                |

tained in 32.7% of cases. The organisms obtained were the following: streptococci 15.3% (*Streptococcus viridans* and *Streptococcus non-hemolyticus*), *Staphylococcus aureus* 2.9%, *B. coli* 9.6%, *B. typhosus* 3.8%, contaminating rods .9%, *B. welchii* and *proteus bacillus* 4.7%, and *ebertella* group .9%. Pure cultures of a single variety of organism occurred in 32 out of the 34 infected cases, 94.1% of the cases in which infection was present.

Cultures of the gall-bladder wall were made in 98 cases. The cultures were positive in 30% of the cases studied. The cultures yielded a single variety of organism in all but two cases, 93.1% of those infected. Streptococci and *B. coli* occurred most frequently. A comparison of these findings with those of other investigators, as shown in Table II, indicates a much smaller percentage of positive cultures in our series. Our low incidence of mixed cultures (2%) compares favorably with that of Kelly (5) Illingworth (7) and Williams and McLachlan (12). The frequency of occurrence of various types of organism found by us in the gall-bladder wall is considerably lower than that of other investigators.

A study of the *gall-bladder bile* obtained at operation was done in 100 cases (Table III). The bile was infected in twenty per cent. Pure cultures occurred in nineteen out of the twenty infected cases or 95%. *B. coli* and streptococci occurred most frequently. *B. typhosus* occurred in 4% of cases and contaminating rods in one case. Our findings are in agreement with those of Judd, Mentzer, and Parkhill (6) as regards frequency of occurrence of *B. coli* and streptococci.

Gall stones were cultured in 26 cases (Table IV). They yielded positive cultures in 31%. Mixed cultures occurred in only 4% of cases. *B. coli* and streptococci were found most frequently. *B. typhosus* occurred once. Judd, Mentzer and Parkhill (6), and Rosenow

(1) also reported *B. coli* and streptococci predominating in cultures of gall stones. In addition, Rosenow (1) found *B. typhosus* in 3% of cases and *B. Welchii* and *proteus bacillus* in 21%.

Cultures of cystic duct lymph nodes in 58 cases (Table V), yielded positive cultures in 22%. Pure cultures were obtained in all but one case in which

occurrence of infection in various parts of the biliary tract. 32.7% of the operative cases showed infection in at least one of the specimens cultured. When infection was present, it occurred in the gall-bladder wall in 85.2% of the infected cases, in the bile in 59%, in the cystic duct node in 38%, and in the calculi in 24% of infected cases.

TABLE II  
Cultures from Wall of Gall-Bladder: Frequency of Infection

|                                      | No. of Cases | Infected | Mixed   | Strep.  | B. Coli | Staph.  | B. Typhosus<br>B. Para Typhosus | B. Welchii<br>B. Proteus | Others  |
|--------------------------------------|--------------|----------|---------|---------|---------|---------|---------------------------------|--------------------------|---------|
|                                      |              | Percent  | Percent | Percent | Percent | Percent | Percent                         | Percent                  | Percent |
| 1935, Authors, Present Series        | 98           | 30       | 2       | 9       | 7       | 3       | 4                               | 3                        | 1       |
| 1916, Rosenow (1)                    | 32           | 84       | 53      | 62      | 37      | 7       |                                 | 7                        | 7       |
| 1919, Brown (29)*                    | 50           | 42       |         | 30      | 18      |         |                                 |                          |         |
| 1919, Brown (29)**                   | 20           | 76       |         | 75      | 15      |         |                                 |                          |         |
| 1926, Kelly-Denver (5)               | 240          | 47       | 1       | 4       | 28      | 4       | 11                              |                          | 3       |
| 1927, Illingworth (7)                | 100          | 62       | 5       | 34      | 17      | 6       |                                 |                          |         |
| 1927, Judd, Mentzer and Parkhill (6) | 200          | 49       | 19      | 13      | 5       | 10      |                                 | 1                        | 20      |
| 1928, Friesleben (30)                | 96           | 76       |         | 14      | 28      | 32      |                                 |                          | 2       |
| 1928, Moynihan (31)                  | 81           | 37       |         |         |         |         |                                 |                          |         |
| 1928, Wilkie, A. L. (8)              | 60           | 12       |         | 4       | 6       |         |                                 | 2                        |         |
| 1929, Branch (10)                    | 210          | 25       |         | 3       | 12      | 4       | .5                              | 2                        | 4       |
| 1930, Gordon-Taylor and Whitby (11)  | 50           | 82       |         | 22      | 18      |         |                                 | 16                       | 26      |
| 1930, Nickel and Judd (9)            | 300          | 50       |         | 22      |         | 13      |                                 |                          | 15***   |
| 1930, Williams and McLauchlan (12)   | 84           | 51       | 5       | 12      | 18      | 12      |                                 | 4                        | 1       |
| 1931, Whipple (13)****               | 178          | 60       |         | 9       | 27      | 16      | 4                               | 3                        | 13      |
| 1932, Magner and Hutcheson (14)      | 200          | 89       |         | 26      | 23      | 23      |                                 | 1                        | 16      |

\*Gall-Bladders showing slight changes.

\*\*Gall-Bladders showing marked changes.

\*\*\*A Bacillus.

\*\*\*\*Tissue not specified.

both *B. coli* and *Streptococcus viridans* were present. Organisms which were found most frequently were streptococci and *B. coli*. Staphylococcus and *B. typhosus* occurred occasionally. Rosenow's (1) percentage of positive cultures is much higher (88%) than ours. He too found streptococci and *B. coli* to occur most frequently.

A study of Table I shows the relative frequency of

Furthermore, the bacteriological study of operative specimens indicated that in 94% of the cases in which infection was present only a single variety of organism was found in cultures from all parts of the biliary tract.

Culture of specimens from the biliary tract of patients coming to operation, while interesting from the pathological standpoint, is manifestly of no value to

TABLE III  
Cultures from Fluid Contents of Gall-Bladder: Frequency of Infection

|                                      | No. of Cases | Infected | Mixed   | Strep.  | B. Coli | Staph.  | B. Typhosus<br>B. Para Typhosus | B. Welchii<br>B. Proteus | Others  |
|--------------------------------------|--------------|----------|---------|---------|---------|---------|---------------------------------|--------------------------|---------|
|                                      |              | Percent  | Percent | Percent | Percent | Percent | Percent                         | Percent                  | Percent |
| 1935, Authors, Present Series        | 100          | 20       | 1       | 6       | 6       | 1       | 4                               |                          | 2       |
| 1903, Hartman (34)                   | 46           | 78       |         | 7       | 54      | 9       |                                 |                          | 9       |
| 1916, Rosenow (1)                    | 29           | 55       | 39      | 24      | 41      | 6       |                                 |                          | 3       |
| 1922, Drennan (2)                    | 100          | 19       | 0       | 2       | 12      | 4       |                                 |                          | 1       |
| 1923, Rovsing (32)                   | 630          | 41       |         |         |         |         |                                 |                          |         |
| 1924, Blalock (3)                    | 270          | 58       | 6       | 3       | 49      | 12      | 19                              |                          | 3       |
| 1925, Johnson (4)                    | 100          | 32       | 4       | 3       | 18      | 7       |                                 |                          | 4       |
| 1927, Illingworth (7)                | 100          | 40       |         | 17      | 21      | 3       |                                 |                          |         |
| 1927, Judd, Mentzer and Parkhill (6) | 193          | 15       | 5       | 7       | 6       | 1       |                                 | .5                       | 4       |
| 1928, Feinblatt (33)                 | 20           | 40       |         | 15      | *       | 5       |                                 |                          |         |
| 1928, Friesleben (30)                | 132          | 47       |         | 11      | 28      |         |                                 |                          | 8       |
| 1928, Moynihan (31)                  | 81           | 31       |         |         |         |         |                                 |                          |         |
| 1928, Wilkie (8)                     | 50           | 12       |         | 4       | 6       |         |                                 | 2                        |         |
| 1929, Branch (10)                    | 210          | 19       | 5       | 3       | 10      | 3       |                                 | 1                        | 2       |
| 1930, Gordon-Taylor and Whitby (11)  | 50           | 32       |         | 8       | 12      |         |                                 | 6                        | 6       |
| 1930, Williams and McLauchlan (12)   | 81           | 47       | 7       | 18      | 12      | 6       | 1                               | 1                        |         |
| 1932, Magner and Hutcheson (14)      | 106          | 33       |         | 7       | 18      | 5       |                                 |                          | 6       |

\*Predominating.

the clinician in making a pre-operative diagnosis. A number of investigators have, therefore, made extensive use of cultures of bile obtained by non-surgical biliary drainage to determine the presence or absence of infection in the biliary tract.

The usability of cultures obtained from the duodenal bile depends upon the fact that the normal duodenum in the fasting state is sterile. This has been stated by numerous investigators, notably MacNeal and Chace (17) who, in 1913, reported a series of cases subjected to non-surgical duodenal drainage. They concluded that: "The normal duodenal fluid during a fast is al-

bacteria (particularly the streptococcus, colon and typhoid groups) or an extensive infection exists noticeably through all the fractions, can we at present stress the significance of our cultural studies."

Piersol and Bockus (21) say that: "The diseased condition of the gall-bladder and bile ducts can be recognized by a microscopic and bacteriological study of the drainage bile which under pathological conditions shows alternations which are significant." Again quoting MacNeal and Chace (17): "It is possible with proper care to obtain a sample of intestinal juice through the duodenal tube sufficiently free from con-

TABLE IV  
*Cultures from Gall Stones: Frequency of Infection*

|                                      | No. of Cases | Infected | Mixed   | Strep.  | B. Coli | Staph.  | B. Typhosus<br>B. Para<br>Typhosus | B. Welchii<br>B. Proteus | Others  |
|--------------------------------------|--------------|----------|---------|---------|---------|---------|------------------------------------|--------------------------|---------|
|                                      |              | Percent  | Percent | Percent | Percent | Percent | Percent                            | Percent                  | Percent |
| 1935. Authors, Present Series        | 26           | 31       | 4       | 12      | 12      |         | 4                                  |                          |         |
| 1898. Gilbert (35)                   | 70           | 33       |         |         |         |         |                                    |                          |         |
| 1916. Rosenow (1)                    | 33           | 88       | 42      | 73      | 12      |         | 3                                  | 21                       | 33      |
| 1927. Illingworth (7)                | 23           | 30       | 0       | 9       | 13      | 9       |                                    |                          |         |
| 1927. Judd, Mentzer and Parkhill (6) | 67           | 36       | 3       | 6       | 3       |         |                                    |                          | 18*     |
| 1929. Branch (10)                    | 94           | 29       |         | 2       | 15      | 6       | 2                                  | 2                        | 2       |
| 1930. Gordon-Taylor and Whitby (11)  | 50           | 28       | 0       | 6       | 12      | 4       |                                    | 6                        |         |
| 1930. Williams and McLachlan (12)    | 41           | 24       | 0       | 5       | 12      | 5       |                                    |                          | 3       |

\*Unidentified bacilli.

most free from living organisms." Twiss and Killian (18) reported a series of control cases in which cultures were made of the duodenal bile. The cultures were reported sterile in practically every case. Among others who have confirmed this fact are Cushing and Livingood (19), Kendall, Day, Walker and Haner (20). Piersol and Bockus (21), and Whipple (22). The latter author summarizes the results of these investigations as follows: "It has been established that in the normal person in the fasting state, the duodenum is collapsed, the little fluid content present is sterile."

The conclusions of practically all investigators in

tamination for bacteriological examination." Whipple (22) states: "That the bile thus obtained through the duodenal tube lends itself to bacteriological study would seem to be a valid surmise, and an organism thus obtained in pure culture might well be considered the etiological factor in the diseased biliary tract."

A. L. Garbat (25) in 1922, advocated the use of sterile duodenal drainage with culture of the bile for typhoid organisms as an additional and more reliable measure for the detection of bile typhoid carriers. Out of 39 duodenal cultures which showed typhoid bacteria, 82% occurred in pure culture. Garbat also reported

TABLE V  
*Cultures from Cystic Duct Lymph Nodes: Frequency of Infection*

|                                   | No. of Cases | Infected | Mixed   | Strep.  | B. Coli | Staph.  | B. Typhosus<br>B. Para<br>Typhosus | B. Welchii<br>B. Proteus | Others  |
|-----------------------------------|--------------|----------|---------|---------|---------|---------|------------------------------------|--------------------------|---------|
|                                   |              | Percent  | Percent | Percent | Percent | Percent | Percent                            | Percent                  | Percent |
| 1935. Authors, Present Series     | 58           | 22       | 2       | 10      | 7       | 2       | 2                                  |                          |         |
| 1916. Rosenow (1)                 | 8            | 88       | 63      | 63      | 25      |         |                                    | 12                       | 12      |
| 1927. Illingworth (7)             | 15           | 40       |         | 20      | 13      |         |                                    |                          | 7       |
| 1927. Wilkie (8)                  | 50           | 90       | 0       | 86      | 2       |         |                                    | 2                        |         |
| 1930. Williams and McLachlan (12) | 43           | 56       | 2       | 16      | 14      | 12      |                                    | 2                        | 9       |

this field are that a carefully performed sterile duodenal drainage is of value in the diagnosis of biliary tract infection. This view point is held by Smithies (23), Lyon and Swalm (24), and many others. In a comprehensive review of non-surgical biliary drainage written in 1921, Smithies is quoted as follows: "Viable colon bacilli were returned by 75.4% of our patients; staphylococci, by 14.9%; streptococci by 5.26% and yeasts, *B. typhosus*, micrococci and unidentified organisms were found in 4.38%. It has seemed to us that only when one fraction of the segmented aspirates contains a predominant increase in a type or group of

(Table VI) 132 bile cultures which did not contain the typhoid bacillus. The items of interest in his figures are: (1) the high percentage of pure typhoid cultures (82%), and (2) the high percentage of sterile cultures (38%).

The only investigators who have reported the results of a bacterial study in detail are Lyon (24, 27), Garbat (25), Buttiaux (26), and Whipple (22). Lyon (24) in 1925, reported a study of 905 non-surgical biliary drainage cultures in 488 patients showing sterile cultures in 15% of cases. The organisms which occurred most frequently were *Staphylococcus aureus*,

*B. coli*, *Streptococcus hemolyticus* and non-hemolyticus.

The investigations of Buttiaux (26) included 50 cases having non-surgical biliary tract drainage (Table VI). He reported 42% sterile cultures. He diluted duodenal bile before plating because he found that freshly drained bile had bactericidal properties.

Correlated studies of both pre-operative bile and operative biliary tract specimens have been reported by Whipple (22) in 1921 and Lyon (27) in 1932. Whipple's series included 25 cases in which cultures of pre-operative drainage bile and cultures of gall-bladder bile, wall, and cystic duct node were obtained. He summarized his findings as follows: "In 50% of the cases, one or more varieties of bacteria found in the pre-operative duodenal bile were present in the gall-bladder bile or gall-bladder tissue at operation. In some of these, however, contaminations are suggested by the variety or type of organism. The presence of *B. subtilis*, *Streptococcus salivarius*, and *Micrococcus catarrhalis* may be regarded as contaminations in the duodenal cultures. On the other hand, the colon bacillus, the hemolytic streptococcus, and *Staphylococcus aureus*, especially if found in the bile following magnesium sulphate instillation, may be considered as

ing. All equipment requiring sterilization was previously autoclaved with the exception of the rubber tube which was boiled to preserve the rubber. Before passing the duodenal tube\*, we routinely passed sterile water through it collecting the washings in a sterile test tube for culture. This served as a check on the sterility of the tube. Our drainages were started at eight-thirty in the morning with a fasting stomach. Whenever possible two or three drainages were performed to serve as an accurate basis for proper interpretation of cultural findings.

A summary of our culture findings in these 222 biliary drainages is shown in Table VI as well as results of other investigators. In this series, 75% positive cultures were obtained and 25% sterile cultures. 56% of the positive cultures were mixed and only 19% showed but one strain of bacteria. The frequency of occurrence of various organisms is shown in Table VI. The predominating organisms were the streptococcus and staphylococcus. The following organisms occurred in 26% of the biliary drainages: *Micrococcus catarrhalis*, the Friedlander bacillus, contaminating rods, yeast, diphtheroids, and *B. pyocyaneus*.

TABLE VI  
Comparison of Bacteriological Findings in Duodenal Drainage: Frequency of Infection

|                               | No. Drainages     | Sterile | Infected | Mixed   | One Strain | Staph.  | B. Coli | Strep. Hemolytic & Non-Hemolytic | B. Typhosus | B. Welchii B. Proteus | Others  |
|-------------------------------|-------------------|---------|----------|---------|------------|---------|---------|----------------------------------|-------------|-----------------------|---------|
|                               |                   | Percent | Percent  | Percent | Percent    | Percent | Percent | Percent                          | Percent     | Percent               | Percent |
| 1935, Authors, Present Series | 222               | 25      | 75       | 56      | 19         | 44      | 8       | 49                               | 1.5         | 2.8                   | 26      |
| 1921, Whipple (22)            | 26                | 15      | 85       | 46      | 39         | 39      | 27      | 46                               |             | 4                     | 30      |
| 1922, Garbat (25)             | (Typhoid) 39      | 0       | 100      | 18      | 62         |         |         |                                  | 100         | .1                    |         |
| 1922, Garbat (25)             | (Non-Typhoid) 132 | 38      | 62       | 16      | 46         | 24      | 32      | 0                                |             |                       | 6       |
| 1925, Lyon (24)               | 905               | 15      | 85       | 23      | 57         | 39      | 36      | 22.6                             | 1           | 0                     | 1       |
| 1931, Buttiaux (26)           | 50                | 42      | 58       |         |            | 3-8     | 5-10    | 6-12                             | 1-2         |                       | 14      |

ctiological factors and as probably present in the gall-bladder or common duct or both if "B" bile is obtained. Furthermore, it is the writer's impression from a study of these cases as well as some 150 cases in which the gall-bladder bile and tissue from the gall-bladder was cultured, that the colon bacillus is the most persistent of the bacteria found in the common duct." Lyon's (27) series of correlated studies consisted of 101 patients who were drained by non-surgical biliary drainage and later came to operation. Lyon states: "In the majority of the cases, the culture obtained at the operating table from the gall-bladder was identical with that recorded in the pre-operative drainage culture."

In 126 of our cases 222 non-surgical biliary drainages were done and cultures made of both the duodenal specimen of bile and the most concentrated specimen obtained after stimulation with magnesium sulphate solution or olive oil.

The method of performing the sterile drainage was that described by Twiss (28). The patient was first required to gargle or spray the throat with argyrol solution (1 dram of 10% argyrol in four ounces of sterile water). The duodenal tube was then passed and the bile collected in sterile bottles. Specimens of 2 c.c. of the various fractions of bile were collected in sterile test tubes and sent to the laboratory for plat-

A comparison of these findings with the operative findings previously reported (Table VII) shows that positive cultures were obtained much more frequently by duodenal drainage than at operation. On the other hand the percentage of cases in which a single variety of organism was found in pure culture was lower in the duodenal drainage than in the operative specimen. Furthermore, there was a different distribution of organisms found in the two series of specimens, for many more varieties of organisms were found in the duodenal drainage than in the operative specimens. These organisms may well be grouped into three categories: (1). Such organisms as *B. typhosus*, *B. coli*, *B. welchii*, and *B. proteus* which normally are not found in the upper gastro-intestinal tract, but which do invade the biliary tract. When found in the bile obtained by duodenal drainage, they afford presumptive evidence of infection of the bile or biliary tract. In typhoid carriers the bile obtained by biliary drainage is usually loaded with *B. typhosus*. Such a finding is pathogenic regardless of the presence of other or contaminating organisms. (2). Such organisms as the Friedlander bacillus, *Micrococcus catarrhalis*, pneumococcus, and yeast which are normal inhabitants of the buccal

\*Rehfuss, Lyon, Levin, and Twiss tubes were used routinely. R. Buttiaux's French duodenal tube was tried and found to be reliable, but due to its fragility its use was abandoned.



cavity, the naso-pharynx, or stomach, but which are not found in cultures of the biliary tract at operation. When these organisms occur in cultures of the bile obtained by duodenal drainage they are presumptive

TABLE VII

Comparison of Bacteriological Findings. Frequency of Infection

|                   | Biliary Tract at Operation | Fluid Contents of Gall-Bladders at Operation | Bile Obtained Prior to Operation by Duodenal Drainage |
|-------------------|----------------------------|----------------------------------------------|-------------------------------------------------------|
| No. of Cases      | 104                        | 100                                          | 126                                                   |
| Sterile Cultures  | Percent 67.3               | Percent 80                                   | Percent 25                                            |
| Infected Cultures | 32.7                       | 20                                           | 75                                                    |

Percentage Frequency of Occurrence of Different Organisms in Cases in Which Positive Cultures Were Obtained.

|                                             | Biliary Tract at Operation | Fluid Contents of Gall-Bladders at Operation | Bile Obtained Prior to Operation by Duodenal Drainage |
|---------------------------------------------|----------------------------|----------------------------------------------|-------------------------------------------------------|
| Total No. of Cases Infected                 | Percent 100                | Percent 100                                  | Percent 100                                           |
| Mixed Cultures                              | 6.2                        | 5                                            | 75                                                    |
| Pure Cultures of Single Variety of Organism | 94.2                       | 95                                           | 25.3                                                  |
| B. Coli                                     | 31.2                       | 35                                           | 10.6                                                  |
| Streptococcus                               | 50                         | 35                                           | 65.0                                                  |
| B. Typhosus                                 | 12.5                       | 20                                           | 2.0                                                   |
| Staphylococcus                              | 9.4                        | 5                                            | 59.0                                                  |
| Contaminating Rods                          | 3.1                        | 5                                            | 4.0                                                   |
| B. Welchii                                  | 15.6                       | 0                                            | 3.7                                                   |
| Eberthella Group                            | .9                         | 0                                            | 0                                                     |
| Micrococcus Catarrhalis                     | 0                          | 0                                            | 17.3                                                  |
| Yeast                                       | 0                          | 0                                            | 14.7                                                  |
| Friedlander's Bacillus                      | 0                          | 0                                            | 4.0                                                   |

evidence of contamination of the latter. (3). Such organisms as streptococci and staphylococci which may infect the biliary tract, but which are also found as normal inhabitants of the buccal cavity, the naso-pharynx, or the stomach. These organisms when found in association with *Micrococcus catarrhalis*, the Friedlander bacillus, pneumococcus, and yeasts likewise are to be considered as contaminants, but when found in pure culture are more likely to indicate infection of the biliary tract. Multiple drainages are of value in determining the significance of such organisms.

The value of cultures of the bile obtained by duodenal drainage is best shown by a study of 48 cases in which pre-operative and operative cultures of bile were made. These results are shown in Table VIII. The percentage of sterile cultures in bile obtained by duodenal drainage was found to be 31; cultures of bile specimens from operated gall-bladders yielded sterile cultures in 73% of cases. In 31 % of the cases bile specimens both prior to operation and at operation were reported sterile. In 23%, the same organism was found in the bile, both before operation and at operation, making a total of 54% of cases in which there was agreement.

In 42% of cases, operative specimens of bile yielded sterile cultures, whereas cultures of bile obtained prior to operation by duodenal drainage contained organisms of various varieties. The organisms found included: *Staphylococcus albus*, *Staphylococcus aureus*, *Streptococcus non-hemolyticus*, *Streptococcus viridans*, *Micrococcus catarrhalis*, the Friedlander bacillus, *B. coli*, *B. proteus*, and yeasts. In 4% of cases the bile obtained by duodenal drainage as well as the bile at

operation yielded a bacterial growth but different organisms. *Duodenal drainage culture findings disagreed with culture findings at operation therefore in 46% of cases.* It is significant to note that when infection of the bile was shown by cultures of the bile taken at operation, positive cultures likewise had been obtained by duodenal drainage. On the other hand, in those cases in which bile at operation was sterile, positive cultures were obtained on duodenal drainage in 42% of cases.

## CONCLUSIONS

(1) The bacteriological examination of specimens removed from the biliary tract at operation furnishes the most accurate information regarding the presence of infection in the biliary tract. Infection was found to be present in 32.7% of the series of 104 cases.

(2) The gall-bladder wall was found to be the seat of infection more often than was the bile, the cystic duct node or calculi.

(3) When infection was found at operation, the organism was usually obtained in pure culture (95%). Streptococci and *B. coli* occurred most frequently. Staphylococcus, *B. typhosus*, *B. welchii* and *B. proteus* occurred less frequently.

(4) A much higher percentage of positive cultures was obtained in cultures of specimens of bile obtained by duodenal drainage than was found in operative specimens. Furthermore, when positive cultures occurred in the drainage bile there was a very high incidence of mixed cultures (75%). Many of these organisms may be regarded as contaminants. Our study of bile cultures both before and at operation in 48 cases showed agreement in 54% of cases, but 46% of the cases showed evidence of contamination of the specimens obtained by duodenal drainage.

(5) The present technique for the bacteriological study of bile obtained by duodenal drainage is unsatisfactory, because of the frequent occurrence in cultures of contaminating organisms from the naso-pharynx, the buccal cavity, or the stomach.

(6) A technique must be developed which will eliminate or reduce to a minimum the confusion due to

TABLE VIII

Comparison of Bacteriological Findings in Pre-Operative Duodenal Drainage Bile with Findings at Operation in 48 Cases

|                                                                                           | No. of Cases | Percent |
|-------------------------------------------------------------------------------------------|--------------|---------|
| Total No. of Cases                                                                        | 48           | 100     |
| Sterile Cultures:                                                                         |              |         |
| At Operation                                                                              | 35           | 73      |
| Duodenal Drainage                                                                         | 15           | 31      |
| Both Specimens Sterile                                                                    | 15           | 31      |
| Same Organism found in both Specimens                                                     | 11           | 23      |
| Culture Findings Prior to Operation that Agree with Findings at Operation                 | 26           | 54      |
| Operative Specimens Sterile. Drainage Infected                                            | 20           | 42      |
| Both Specimens Infected, but with Different Organisms                                     | 2            | 4       |
| Drainage Sterile, Positive Culture at Operation                                           | 0            | 0       |
| Culture Findings Prior to Operation that were not in Agreement with Findings at Operation | 22           | 46      |

the presence of such contaminating organisms before cultures of bile obtained by duodenal drainage can be depended upon to supply reliable evidence of infection of the biliary tract.

## REFERENCES

- Rosenow, E. C.: The etiology of cholecystitis and gall-stones and their production by intravenous injection of bacteria. *J. Infect. Dis.*, 19:527-556, 1916.
- Dreanan, J. G.: Bacteriological study of fluid contents of 100 gall-bladders removed at operation. *Ann. Surg.*, 76:482, 1922.
- Blalock, Alfred: A statistical study of 888 cases of biliary tract disease. *Johns Hopkins Hospital Bulletin*, 35:391-409, 1924.
- Johnson, W. O.: One-hundred consecutive cholecystectomies. *Am. J. M. Sc.*, 170:181-185, 1925.
- Kelly, A. O. J.: Quoted by: Osler, William: Modern medicine. New York, Lea & Febiger, 1926, Vol. 3, pp. 841-842, 3 ed.
- Judd, E. S.; Mentzer, S. H., and Parkhill, E.: Bacteriologic study of gall-bladders removed at operation. *Am. J. M. Sc.*, 173:16, 1927.
- Hillingworth, C. F. W.: Types of gall-bladder infection. *Brit. J. Surg.*, 15:223, 1927.
- Wilkie, A. L. (of Montreal. From Clinic of Professor D. P. D. Wilkie of Edinburgh). *British Jour. of Surg.*, 15:450-465, 1927-28.
- Nickel, Allen C., and Judd, E. Starr (Mayo Clinic) Cholecystitis: A Bacteriologic and Experimental study of three hundred surgically resected gall-bladders. *S. G. O.*, L 655-662, 1930.
- Branch, Charles F. (From Massachusetts Homeopathic Hospital): A bacteriological study of a group of diseased gall-bladders. *New Eng. J. of Medicine*, 201:308-312, 1929.
- Gordon-Taylor, G., and Whitby, L. E. H.: A bacteriological study of 50 cases of cholecystectomy with special reference to anaerobic infections. *Brit. J. Surg.*, 18:78, 1930.
- Williams, B., and McLachlan, D. G. S.: Etiology of Cholecystitis-Bacteriological observations. *Lancet*, 2:342, 1930.
- Whipple, Allen O.: Bacteriology of biliary tract lesions. Nelson Loose-Leaf Living Surgery.
- Magner, William, and Hutcheson, J. M.: (Toronto) Cholecystitis (Bacteriological and experimental study). *Canadian Med. Assoc. J.*, 27:469-476, 1932.
- Rehuss, Martin, E., and Nelson, Guy M.: *Amer. Jour. of Digest. Dis. and Nutr.*, Vol. 1, 759-768, 1935.
- Carter, R. F.; Greene, C. H., and Twiss, J. R.: Diagnosis and treatment of diseases of the biliary tract: Methods employed in the clinic for diseases of the liver and biliary tract of the N. Y. Post-Graduate Hospital.
- MacNeal, W. J., and Chace, A. F.: A contribution to the bacteriology of the duodenum. *Arch. Int. Med.*, 12:178, 1913.
- Twiss, J. R., and Killian, J. A.: Diagnostic Methods of Metabolic Studies in Disease of the Biliary Tract. (1) Description of the routine examination and discussion of normal standards. *Am. J. Med. Sci.*, 186:418, Sept., 1933.
- Cushing, Harvey, and Livingood, Louis E.: Contributions to the Science of Medicine, p. 543, 1900.
- Kendall, A. J.; Day, A. A.; Walker, A. W., and Hancr, A. C.: The bacteriology and chemistry of adult duodenal contents. *J. Infect. Dis.*, 40:677, 1927.
- Piersol, Geo. M., and Bockus, H. L.: A study of the bile obtained by non-surgical biliary drainage, with special reference to its bacteriology. *Am. J. M. Sc.*, 165:486-497, April, 1923.
- Whipple, A. O.: The use of the duodenal tube in the pre-operative study of the bacteriology and pathology of the biliary tract and pancreas. *Ann. Surg.*, 73:556, 1921.
- Smithies, Frank; Karshner, Clyde F., and Oleson (Chicago): Non-surgical drainage of the biliary tract. *J. A. M. A.*, 2036-2042, 1921.
- Lyon, B. B. V. and Swalm, W. A.: The therapeutic value of non-surgical drainage of the biliary tract. *J. A. M. A.*, 85:1541-1548, 1925.
- Garbat, A. L.: Typhoid carriers and typhoid immunity. New York, Rockefeller Institute for Medical Research, 1922. (*Monograph of Rockefeller Inst. for Med. Research*, No. 16).
- Huttlax, R.; Piette, G., and Chavy, A.: Dispositif permettant le prelevement aseptique des biles humaines par tubage duodenal. *Arch. d. mal. de l'app. digestif.*, 21:619-622, 1931.
- Lyon, B. B. V.: The bacteriology of bile obtained by duodenal tube drainage. *J. Lab. and Clin. Med.*, 17:583, 1932.
- Twiss, J. R.: Technic of non-surgical drainage of the biliary tract. *J. A. M. A.*, 100:792-793, 1933.
- Brown, R. O.: A study on etiology of cholecystitis and its production by injection of streptococci. *Arch. Int. Med.*, 23:185-189, 1919.
- Friesleben, M.: Bakteriologische Befunde bei extirpierten Gallenblasen. (Mit besonderer Berücksichtigung der Entero kokkenbefunde). *München Med. Wechnchr.*, 75:81-83, Jan. 13, 1928.
- Moynihan, Sir Berkeley: The gall-bladder and its infections. *British Med. Jour.*, pp. 1-6, Jan. 7, 1928.
- Rovsing, T.: *Acta Chir Scandinav.*, 56:103, 1923.
- Feinblatt, Henry M.: The infrequency of primary infection in gall-bladder disease. A study of 400 gall-bladders removed at operation. *New Eng. Jr. of Med.*, 199:1073, 1928.
- Hartmann (1903) Quoted by Gordon-Taylor, S., and Whitby, L. E. N. *Brit. Jr. Surg.*, 18:78, July, 1930.
- Gilbert (1898) Quoted by Gordon-Taylor, S., and Whitby, L. E. N. *Brit. Jr. Surg.*, 18:78, July, 1930.

## Calculating the Diagnostic Value of Gastric Analysis: A Study in the Methodology of Diagnosis \*

FRANCES R. VANZANT, M.D.\*\*

and

WALTER C. ALVAREZ, M.D.

ROCHESTER, MINNESOTA

**R**ECENTLY there came to The Mayo Clinic a physician with the story that he had been well all his life up to the week before, when, at the age of sixty years, he began to suffer with epigastric pain and indigestion. The roentgenologists saw a lesion which they thought was on the gastric side of the pyloric ring, and probably benign. Gastric analysis disclosed free acid of sixty units.

Now, what was to be done? With a short history at the age of sixty, the probability of the lesion's being a carcinoma was great, but just how great it was no one knew. The high acidity spoke for duodenal ulcer, but the report of the roentgenologist was against this. Summing up the several probabilities as best they could, the consultants who saw the man came to the conclusion that the likelihood of the lesion's being on the gastric side, and malignant, was too large for comfort, and since the probability of surviving an exploratory

laparotomy performed by the surgeon chosen to do the work is better than 99 to 1, the patient cheerfully accepted the operation. Fortunately, the lesion proved to be a duodenal ulcer that could be excised, and when last heard from, the man was doing well.

This brief case report will serve to illustrate the main point that concerns us, and this is that when a man's very life hangs on the wisdom of a single decision, we physicians must often base it on a crude sort of mental arithmetic in which we balance probabilities, some in favor of one course and others against it. When one considers the fact that we only guess at the size of the several probabilities, and that few of us have any conception of the nature of the mathematics to be employed in combining them, the marvel is that diagnoses today are as correct as they often are.

In this paper we offer some figures which we believe will help in the solution of one of these problems, which arises every day in the practice of a gastroenterologist, and incidentally, we hope to contribute

\*This work was aided by a grant from the Josiah Macy, Jr., Foundation.

\*\*Now residing in Houston, Texas.

Submitted August 22, 1935.

something to the methodology of diagnosis as a whole. What we have done here is to calculate the probabilities that a patient at The Mayo Clinic, of a certain age and sex, and with a certain gastric acidity, (one hour after eating eight Sunshine brand arrowroot cookies and drinking 400 c.c. of water), has either a gastric carcinoma, a gastric ulcer, a duodenal ulcer, or one of a residual group of "other diseases" and neuroses.

We would have been better pleased if we could have observed the actual frequency with which the different diseases appear in men and women separately, at different ages, and with different gastric acidities, but this would have required analysis of thousands of records. For instance, we found on calculation that in order to secure a case of gastric carcinoma with hyperacidity among women aged from seventy to seventy-nine years, we would have had to search through the records of about 100,000 clinic patients. Naturally,

due not only to the relative incidences of the two diseases throughout the United States, but to other imponderable factors which bring to this clinic more patients with one disease than with another.

The sex of a patient also has an important influence on the probabilities under consideration because, in the United States, peptic ulcer and gastric carcinoma tend to appear from three to five times more frequently in men than in women.

Highly important also is the factor of age because, obviously, a young man is more likely to be suffering with duodenal ulcer than with gastric carcinoma while an old man is more likely to have a carcinoma. The next step, therefore, was to introduce this factor of age; the probabilities had to be calculated, and then used to modify those already computed.

If we had had a sufficient number of data we would have divided each of the eight main groups in Table 1

TABLE I

*Diagnoses made in the cases of 1052 patients who submitted to gastric analysis one after the other at The Mayo Clinic in the autumn of 1932*

| Disease           | Entire group |          |       |          | With free acid |          |       |          | Without free acid |          |       |          |
|-------------------|--------------|----------|-------|----------|----------------|----------|-------|----------|-------------------|----------|-------|----------|
|                   | Men          |          | Women |          | Men            |          | Women |          | Men               |          | Women |          |
|                   | No.          | Per cent | No.   | Per cent | No.            | Per cent | No.   | Per cent | No.               | Per cent | No.   | Per cent |
| Gastric carcinoma | 33           | 5.3      | 6     | 1.4      | 6              | 1.2      | 3     | 0.8      | 27                | 22.1     | 3     | 4.8      |
| Gastric ulcer     | 6            | 1.0      | 5     | 1.2      | 5              | 1.0      | 3     | 0.8      | 1                 | 0.8      | 2     | 3.2      |
| Duodenal ulcer    | 126          | 20.1     | 45    | 10.5     | 125            | 24.9     | 43    | 11.8     | 1                 | 0.8      | 2     | 3.2      |
| Other diseases    | 450          | 73.6     | 371   | 86.9     | 367            | 72.9     | 315   | 86.6     | 93                | 0.3      | 56    | 88.8     |
| Total             | 625          | 100.0    | 427   | 100.0    | 503            | 100.0    | 364   | 100.0    | 122               | 100.0    | 63    | 100.0    |

the gathering of so many cases is practically impossible. And hence it is that several of the probabilities which we needed in our calculations had to be derived indirectly, with the help of certain plausible assumptions based on the analysis of thousands of data which we have been gathering during the last five years.

We would emphasize again that in this analysis the relevant factors are four: (1) the fact that a patient came to The Mayo Clinic and submitted to gastric analysis after an Ewald meal of a certain type; (2) the sex of the patient; (3) his or her age, and (4) the degree of his or her gastric acidity.

We began by finding the percentage incidence, in our material, of patients with gastric carcinoma, gastric ulcer, duodenal ulcer, and a residual group of "other diseases" (see Table 1). We next calculated the probable incidence of the four types of disease in each decade of life (see table 3), and finally, we calculated the probable distribution of four grades of acidity in men and women, at different ages, affected with the four types of disease. The reader who is not interested in the details of these processes will probably want to skip the following section on method.

#### METHOD

The calculations which led to the construction of Figure 1, A and B, began with the making of Table 1, which shows the percentages of the men and women, examined during a certain period, in the gastric laboratory of The Mayo Clinic, who were found to be suffering with gastric cancer, benign gastric ulcer, duodenal ulcer, or one of a residual group of "other diseases."

From this table it will be seen that, given only the fact that a man is referred to the gastric laboratory of The Mayo Clinic, one can say, for instance, that the chances are twenty to one that his indigestion is due to a duodenal rather than to a gastric ulcer. This is

(four diseases and two sexes) into six groups according to the ages in decades of the patients, but as this was impossible, we had to assume that the age distributions in the case of each of the four different types of disease were the same as those already determined for hundreds of Mayo Clinic patients suffering with (a) duodenal ulcer, (b) gastric ulcer, and (c) gastric cancer. As was to be expected, the age distribution of the patients with "other" nongastric diseases was practically that of the run of clinic patients whose age distribution we knew (1). These four\* age distributions are given in Table 2.

To illustrate the arithmetic of the next step we will take as an example the first column in table 3. Beginning with the corresponding column in Table 2, we multiplied the first of the four percentage frequencies, which happens to be for carcinoma in men aged from twenty to twenty-nine years, by 5.3, which represents the percentage incidence (from Table 1) of gastric carcinoma in a hundred men of all ages coming to the gastric laboratory of The Mayo Clinic.

The next figure in Table 2 was multiplied by the next figure in Table 1, which represents the incidence of gastric ulcer, and so on. In this way, we obtained four numbers which were proportional to the probabilities of the incidence of the four types of disease in men, aged from twenty to twenty-nine years, who had submitted to gastric analysis at The Mayo Clinic. Since it would make no difference in the estimation of relative probabilities if each of these numbers were to be multiplied by a constant, we multiplied them by a factor which made their sum 100 and thereby reduced them to percentages. The procedure was then repeated

\*Actually there were eight distributions, but for the sake of brevity, we will not keep repeating that there were two sets of data, one for men and one for women, each treated separately.

until similar percentage probabilities were calculated for the other eleven age groups listed in Table 3.

We come now to the problem of introducing the last factor into the calculation, namely that of gastric acidity. Again we had to resort to indirect computation because our groups of cases were not large enough for repeated subdivision. What we needed were percentage distributions of gastric acidity for the two sexes, for each of six decades of life and for each of

of disease. We say three because no shift was needed for the residual group of "other diseases."

Each of the twenty-four acidity distributions (four disease groups and six decades) was then split arbitrarily into four zones representing achlorhydria, hypochlorhydria, euclorhydria, and hyperchlorhydria. To define the limits of euclorhydria, we marked off approximately the value of one standard deviation above and below the mean for acidity at middle age.

TABLE II

*Percentage distributions by ages for men and women with the four types of disease being studied\**

| Disease                              | Men        |       |       |       |       |       | Cases | Mean | S. D. |
|--------------------------------------|------------|-------|-------|-------|-------|-------|-------|------|-------|
|                                      | Age, years |       |       |       |       |       |       |      |       |
|                                      | 20-29      | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 |       |      |       |
| Gastric carcinoma                    | 2.0        | 12.6  | 31.7  | 35.5  | 15.1  | 2.8   | 1671  | 55.7 | 10.2  |
| Gastric ulcer                        | 6.7        | 21.7  | 33.5  | 25.8  | 9.5   | 1.7   | 393   | 46.2 | 11.4  |
| Duodenal ulcer                       | 11.8       | 33.8  | 30.5  | 17.6  | 5.6   | 0.4   | 1749  | 42.4 | 11.2  |
| "Other diseases"                     | 7.2        | 20.1  | 31.1  | 25.7  | 11.4  | 2.7   | 625   | 46.9 | 12.4  |
| Disease                              | Women      |       |       |       |       |       | Cases | Mean | S. D. |
|                                      | Age, years |       |       |       |       |       |       |      |       |
|                                      | 20-29      | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 |       |      |       |
| Gastric carcinoma                    | 2.2        | 11.0  | 27.2  | 33.0  | 19.6  | 5.9   | 415   | 52.8 | 11.5  |
| Gastric ulcer                        | 5.9        | 20.4  | 34.3  | 26.7  | 10.0  | 1.8   | 107   | 46.8 | 11.2  |
| Duodenal ulcer                       | 10.6       | 32.2  | 31.7  | 18.8  | 5.8   | 0.5   | 446   | 43.5 | 11.7  |
| "Other diseases"                     | 7.2        | 19.9  | 30.7  | 25.5  | 11.8  | 2.6   | 427   | 47.0 | 12.6  |
| Actual figures for gastric carcinoma |            |       |       |       |       |       |       |      |       |
| Men                                  | 11         | 110   | 332   | 617   | 498   | 102   |       |      |       |
| Women                                | 5          | 60    | 110   | 128   | 102   | 19    |       |      |       |

\*In the cases of gastric carcinoma, gastric ulcer and "other diseases," smoothed values are given, computed from the normal curve based on the mean and S. D. The distribution of data from cases of duodenal ulcer is so skewed that the actual figures had to be used. We would have avoided a slight error by using actual figures in the case of carcinoma because this distribution is also slightly skewed. The actual figures are given for the sake of those who may wish to calculate their own Table VII

the four disease groups. We arrived at these figures as follows. In a previous study of several thousand persons (7) we constructed percentage distributions showing normal gastric acidity in the two sexes and in the several decades of life. In subsequent studies we found that, in our material, the percentage distributions of gastric acidity in the several diseases resemble closely those of normal persons except as they are shifted a certain distance to the right or left along the abscissal line representing acidity. There are also differences in the percentage incidence of achlorhydria. These deviations from normal are epitomized in Tables 4 and 5 (2, 6).

TABLE III

*Percentages of persons in each decade (submitting to gastric analysis) who were found to be suffering with one of several diseases, based on a study of 1052 patients with and without free gastric acid. The figures represent percentages of each age group*

| Disease           | Men        |       |       |       |       |       |
|-------------------|------------|-------|-------|-------|-------|-------|
|                   | Age, years |       |       |       |       |       |
|                   | 20-29      | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 |
| Gastric carcinoma | 0.8        | 2.5   | 6.7   | 9.7   | 12.3  | 12.9  |
| Gastric ulcer     | 1.6        | 0.8   | 1.1   | 0.9   | 0.6   | 0.9   |
| Duodenal ulcer    | 29.4       | 22.5  | 19.7  | 18.1  | 18.7  | 68.9  |
| Other diseases    | 68.2       | 74.2  | 73.6  | 71.3  | 68.4  | 17.3  |
| Total             | 100.0      | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| Disease           | Women      |       |       |       |       |       |
|                   | 20-29      | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 |
| Gastric carcinoma | 0.4        | 0.5   | 0.7   | 1.4   | 3.3   | 8.6   |
| Gastric ulcer     | 0.8        | 0.7   | 0.7   | 0.9   | 1.3   | 1.8   |
| Duodenal ulcer    | 16.7       | 11.7  | 9.6   | 10.0  | 12.4  | 17.9  |
| Other diseases    | 82.1       | 87.1  | 89.0  | 87.7  | 83.0  | 71.6  |
| Total             | 100.0      | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |

We felt, therefore, that we could safely take the normal (acid) distributions for age and sex and shift them to the right or left to show the probable distributions of acidity in patients with the three types

Because of the differences between the acidities of men and women, shown by Vanzant and others (7), it seemed necessary to assign different limiting values for these zones in the two sexes. The values chosen were:

|           | Achlorhydria | Hypochlorhydria | Euclorhydria | Hyperchlorhydria |
|-----------|--------------|-----------------|--------------|------------------|
| For men   | 0            | 1-29            | 30-59        | above 60         |
| For women | 0            | 1-19            | 20-44        | above 45         |

The figures represent units of free hydrochloric acid.

Table 5 gives the incidence of achlorhydria found at the end of one hour after our type of test meal in a large number of cases of the three diseases listed. The figures represent percentages of that incidence of achlorhydria which would be expected in a group of apparently normal persons with a similar age distribution. (For technic of obtaining these figures, see Vanzant (4)).

An example of the arithmetic of the final steps of the work is shown in Table 6 where we give the successive calculations by which we derived the first four figures of Table 7. It will be seen that the procedure is the same as already described for step 2. We turned

TABLE IV

*The number of units by which the acidity distribution for normal persons is shifted in the case of the three diseases listed*

| Disease           | Men   | Women |
|-------------------|-------|-------|
| Gastric carcinoma | -14.0 | -8.7  |
| Gastric ulcer     | -5.4  | -6.6  |
| Duodenal ulcer    | +12.3 | +11.1 |

first to our tables showing the distributions of acidities in the two sexes, at the different ages, and with the four types of disease, and found the number of men aged from twenty to twenty-nine years, who would be

expected not to show free acid in the stomach. The four figures there found were multiplied by the corresponding figures in the first column of table 3 showing the incidence of the several diseases in men in this

TABLE V

*Incidence of achlorhydria found at the end of one hour after an Ewald type of meal\**

| Disease           | Percent |       |
|-------------------|---------|-------|
|                   | Men     | Women |
| Gastric carcinoma | 341     | 275   |
| Gastric ulcer     | 78      | 92    |
| Duodenal ulcer    | 10      | 12    |

\*The figures represented percentages of the incidence of achlorhydria to be expected in a group of apparently normal persons with the same age distribution.

age group, and the four results were multiplied by a factor which enabled us to express them as percentages of their sum. This process was repeated many times until Table 7 was completed. Figure 1, A and B, represents graphically the data tabulated in Table 7.

### CAUTIONS

We probably should again emphasize the fact that the probabilities given here apply only to those patients at The Mayo Clinic who, for one reason or another, were sent for gastric analysis. In addition to this, the probabilities are based on age, sex, and the amount of free acid found in the stomach one hour after a certain type of test meal. Naturally, then, the figures in Table 7 are not necessarily applicable to the solving of diagnostic problems in patients seen at another clinic, and they certainly do not apply when the acidity of the stomach is studied after the injection of histamine. It must be obvious, also, that the minute the patient gives a history or submits to roentgenologic examination, other probabilities enter in to modify the diagnostic problem, probabilities which no one has as yet measured accurately or stated numerically.

As we have pointed out elsewhere (4), a single gastric analysis has a large probable error, and hence, when using Table 7, the physician can only hope that the usual variation up or down will still leave a single reading within its usual zone of acidity.

It should be obvious that anyone who wishes to use the figures given in Table 7 must first make sure that the incidence of the several diseases in his clinical material is much the same as it is in patients seen at The Mayo Clinic. He must also be using an Ewald type of meal similar to the one that we use. The incidence of the diseases at different ages and the relation of acidity to age are probably much the same in different clinics, but the number of patients seen with the different diseases may perhaps vary so much in the practices of different gastro-enterologists that each man will have to modify Table 7 to suit his own clinical material.

Anyone who wishes to make his own table should first make a table comparable with our Table 1, based on his own clinical material. If then, for instance, in the case of the "entire group," he should find that the percentage of occurrence of gastric carcinoma in men, instead of being 5.3 per cent, as in our material, is 7.2 per cent, he could multiply each one of the figures for carcinoma with achlorhydria in Table 7 by the fraction  $7.2/5.3$ . If, in his material, the percentage of gastric carcinoma with free acid should be found to be 2.3 in-

stead of 1.2 per cent, he would multiply, one after the other, the figures for carcinoma with hypochlorhydria, euclorhydria, and hyperchlorhydria by the fraction  $2.3/1.2$ .

### COMMENT

One of the most striking features to be noted in Figure 1 is the evidence pointing to the rarity of gastric ulcer. In Table 1, we see that for one man with gastric ulcer, there were five with gastric carcinoma and twenty with duodenal ulcer. Obviously the odds are against the physician who assumes, as so many do, that a gastric lesion seen with the roentgenoscope is probably benign. Table 3 shows the interesting shifts in the odds which come with advancing years. Thus, if a thousand men in their twenties come to The Mayo Clinic and are sent for gastric analysis, these three postulates alone make it probable that eight will be suffering with gastric carcinoma; sixteen with gastric ulcer; 294 with duodenal ulcer, and 682 with some non-gastric or functional trouble. But if one takes a thousand similar male patients, all older than seventy years of age, approximately 129 will have gastric cancer, nine will have gastric ulcer, and 173 will have duodenal ulcer.

Any of these probabilities will, of course, be altered markedly the minute the patient gives his history, and they will be altered again as his physical examination is made and as his laboratory and roentgenologic reports come in. Thus, if a man aged twenty-five years suffering with indigestion is found to lack free acid, his chances of having a gastric carcinoma are quadrupled, while if his stomach is found to be hyperacid, his chances of having cancer are reduced almost to zero, and his chances of having a duodenal ulcer are somewhat increased. If, now, he complains of hunger pain, and the roentgenologist sees a crater-form defect in the duodenum, the chances of his having an ulcer become very high.

TABLE VI

*An example of the calculations by which were derived the first four figures at the top of the first column in table VII*

|                                                                                                                                               | Gastric carcinoma | Gastric ulcer | Duodenal ulcer | Other diseases | Total |
|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------|---------------|----------------|----------------|-------|
| a. Frequency of occurrence of achlorhydria in men aged from 20 to 29 years and suffering with the diseases listed.                            | 3.4               | 0.8           | 0.1            | 1.0            |       |
| b. Frequency of the occurrence at The Mayo Clinic of the several diseases; male patients aged from 20 to 29 years. See Table 3, first column. | 0.8               | 1.6           | 29.4           | 68.2           |       |
| a x b                                                                                                                                         | 2.72              | 1.28          | 2.94           | 68.2           | 75.14 |
| Percentages representing probable occurrence of the several diseases in men aged from 20 to 29 years with achlorhydria.                       | 3.6               | 1.6           | 3.9            | 90.9           | 100.0 |

One of the many interesting things to be learned from Table 7 and Figure 1 is the high degree of probability that a man aged seventy years or more with hyperchlorhydria is suffering with duodenal ulcer.

Figure 1 shows the increasing diagnostic value of hyperchlorhydria with advancing years. As one would expect from the greater susceptibility of men to ulcer, the significance of hyperacidity is greater in men than in women, but curiously, this sexual difference does not stand out until the fourth decade of life.

The importance of studies such as these can be seen particularly when one examines some of the differences between the probabilities for men and women. For instance, in the fifth decade of life, if a man and his sister are suffering with indigestion and are found to be achlorhydric, he will have a 20 per cent chance of

to about forty-five years, and then falls. Curiously, the difference between the percentages of nongastric disease in men and women is fairly constant until the eighth decade of life when it is almost wiped out.

In Table 7, it should be noted how little diagnostic value achlorhydria has in the first forty years of life, and particularly in women. The difficulty is that an anacid stomach is to be found so commonly in apparently normal persons. Its diagnostic value is greatest, perhaps, in the occasional case of early macrocytic anemia in which the blood picture or the nervous lesions are not quite characteristic.

TABLE VII

*Percentages of men and women referred to the gastric laboratory of The Mayo Clinic in different decades of life and with different grades of gastric acidity who are likely to be suffering with gastric carcinoma, gastric ulcer, duodenal ulcer, or some other disease\**

| Disease           | Men           |                  |                |                   | Women         |                  |                |                   |
|-------------------|---------------|------------------|----------------|-------------------|---------------|------------------|----------------|-------------------|
|                   | Achlor-hydria | Hypochlor-hydria | Euchlor-hydria | Hyperchlor-hydria | Achlor-hydria | Hypochlor-hydria | Euchlor-hydria | Hyperchlor-hydria |
| Age 20-29         |               |                  |                |                   |               |                  |                |                   |
| Gastric carcinoma | 3.6           | .7               | .2             | .1                | 1.9           | 1.0              | .4             | .1                |
| Gastric ulcer     | 1.6           | 1.8              | 1.1            | .5                | 1.2           | 2.0              | .8             | .3                |
| Duodenal ulcer    | 3.9           | 6.4              | 17.2           | 38.1              | 1.9           | 5.0              | 13.7           | 33.9              |
| Other diseases    | 90.9          | 91.1             | 81.5           | 61.4              | 95.0          | 92.0             | 85.1           | 65.7              |
| Total             | 100.0         | 100.0            | 100.0          | 100.0             | 100.0         | 100.0            | 100.0          | 100.0             |
| Age 30-39         |               |                  |                |                   |               |                  |                |                   |
| Gastric carcinoma | 10.0          | 1.7              | .4             | .1                | 2.6           | 1.2              | .4             | .2                |
| Gastric ulcer     | .7            | 1.7              | 1.0            | .4                | 1.1           | 1.4              | .6             | .3                |
| Duodenal ulcer    | 2.8           | 8.2              | 21.2           | 44.4              | 1.3           | 3.1              | 9.5            | 25.2              |
| Other diseases    | 86.5          | 88.4             | 77.9           | 55.1              | 95.0          | 94.3             | 89.5           | 74.3              |
| Total             | 100.0         | 100.0            | 100.0          | 100.0             | 100.0         | 100.0            | 100.0          | 100.0             |
| Age 40-49         |               |                  |                |                   |               |                  |                |                   |
| Gastric carcinoma | 20.3          | 4.2              | 1.1            | .3                | 3.8           | 1.6              | .6             | .2                |
| Gastric ulcer     | .6            | 2.1              | 1.1            | .5                | 1.1           | 1.4              | .6             | .3                |
| Duodenal ulcer    | 2.0           | 7.2              | 19.9           | 42.7              | 1.1           | 2.5              | 7.8            | 21.3              |
| Other diseases    | 77.1          | 86.5             | 77.4           | 56.5              | 94.0          | 94.5             | 91.0           | 78.2              |
| Total             | 100.0         | 100.0            | 100.0          | 100.0             | 100.0         | 100.0            | 100.0          | 100.0             |
| Age 50-59         |               |                  |                |                   |               |                  |                |                   |
| Gastric carcinoma | 31.0          | 6.6              | 1.9            | .5                | 7.1           | 3.2              | 1.1            | .4                |
| Gastric ulcer     | .7            | 1.7              | 1.1            | .4                | 1.3           | 1.7              | .9             | .4                |
| Duodenal ulcer    | 1.7           | 10.8             | 25.0           | 46.9              | 1.1           | 2.6              | 8.1            | 22.2              |
| Other diseases    | 66.6          | 80.9             | 72.0           | 52.2              | 90.5          | 92.5             | 89.9           | 77.0              |
| Total             | 100.0         | 100.0            | 100.0          | 100.0             | 100.0         | 100.0            | 100.0          | 100.0             |
| Age 60-69         |               |                  |                |                   |               |                  |                |                   |
| Gastric carcinoma | 37.2          | 8.5              | 2.7            | .3                | 15.4          | 6.6              | 3.1            | 1.2               |
| Gastric ulcer     | .4            | 1.1              | .6             | .4                | 1.8           | 2.3              | 1.3            | .6                |
| Duodenal ulcer    | 1.8           | 16.4             | 33.6           | 56.1              | 1.3           | 4.0              | 10.2           | 23.8              |
| Other diseases    | 60.6          | 74.0             | 63.1           | 43.2              | 81.5          | 87.1             | 85.4           | 74.4              |
| Total             | 100.0         | 100.0            | 100.0          | 100.0             | 100.0         | 100.0            | 100.0          | 100.0             |
| Age 70-79         |               |                  |                |                   |               |                  |                |                   |
| Gastric carcinoma | 38.2          | 10.2             | 2.4            | .4                | 35.3          | 17.6             | 8.0            | 2.8               |
| Gastric ulcer     | .6            | 2.5              | 1.2            | .5                | 2.3           | 3.2              | 1.7            | .8                |
| Duodenal ulcer    | 1.5           | 16.3             | 38.8           | 64.7              | 1.8           | 5.2              | 15.0           | 34.6              |
| Other diseases    | 59.7          | 71.0             | 57.6           | 34.4              | 60.6          | 74.0             | 75.3           | 61.8              |
| Total             | 100.0         | 100.0            | 100.0          | 100.0             | 100.0         | 100.0            | 100.0          | 100.0             |

\*Values: Hypochlorhydria for men, 1-29; for women, 1-19.

Euchlorhydria for men, 30-59; for women, 20-44.

Hyperchlorhydria for men, 60 and above; for women, 45 and above.

suffering with carcinoma of the stomach, while she will have only about a 4 per cent chance. After the age of seventy, their danger will be about equal, and represented by a figure of about 37 per cent.

So far as we know these important probabilities have never been expressed numerically before. The nearest approach to such an analysis known to us was attempted by MacLagan (3) who unfortunately did not have enough data at hand to solve the problems which he had the vision to outline.

Table 1 shows that in approximately three out of four men and five out of six women with indigestion, no disease can be demonstrated in stomach or duodenum. What surprised us was that in men and women the percentage of nongastric disease rises with age up

## NEW LIGHT NOW ON THE PROBLEM OF THE PHYSICIAN WITH A PYLORIC LESION

To return now to the problem of the physician whose case we described at the beginning of this paper: On turning to Table 7, it will be seen that solely on the basis of his sex, his age, and his hyperacidity, there were 561 chances in 1,000 of his having a duodenal ulcer against three chances in a 1,000 of his having a gastric cancer. The unfortunate feature was that we did not have, and for that matter, we still do not have, figures with which to express the probability that the roentgenologist might be mistaken as to his location of the lesion, and we did not have then, and we still do not have, statistics that would enable us to appraise the value of a short history of indigestion at different



## Men

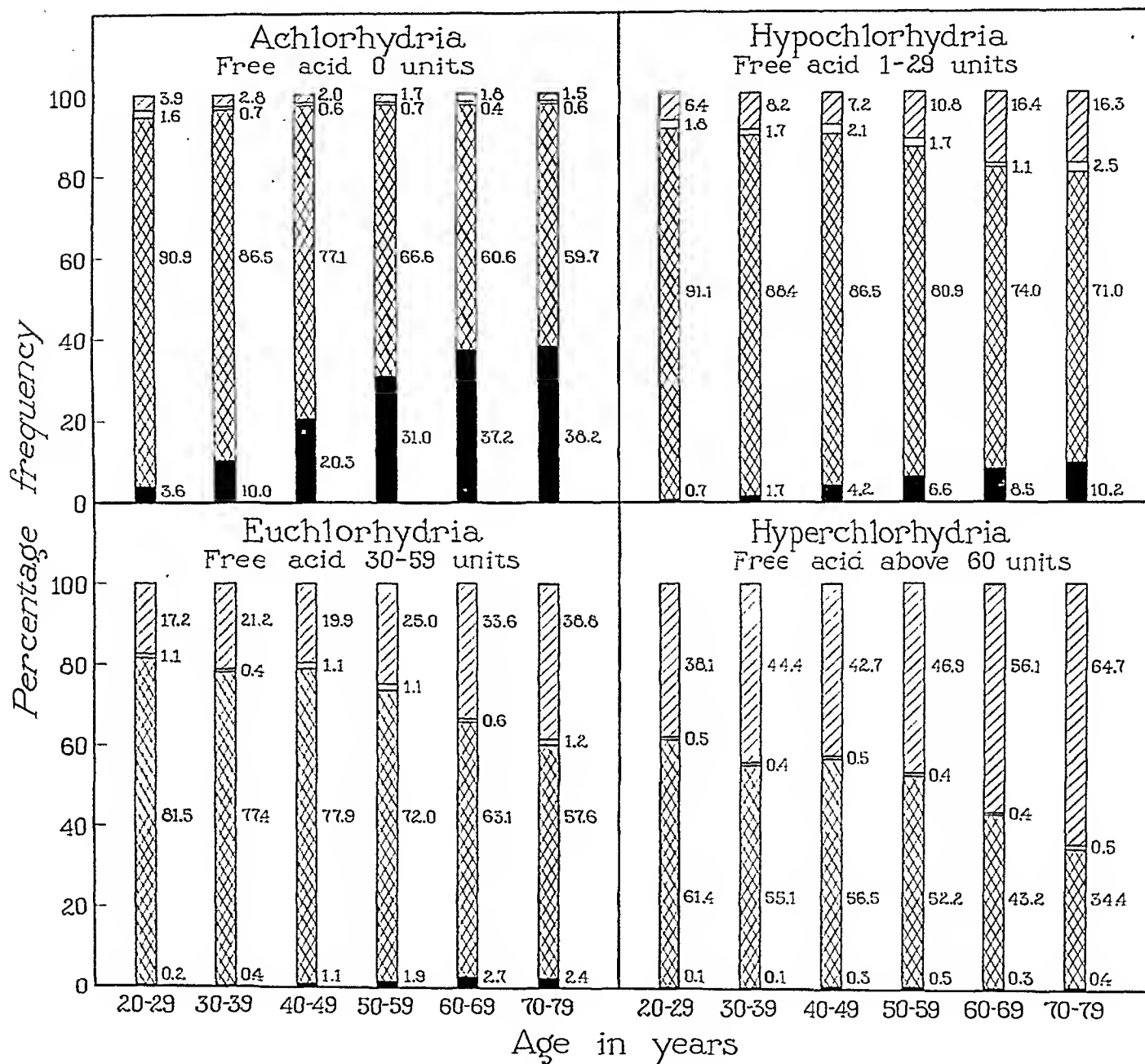


Fig. 1a. Percentage incidence of duodenal ulcer, gastric ulcer, and gastric carcinoma in men of different ages with achlorhydria, hypochlorhydria, euchlorhydria, and hyperchlorhydria. In the residual group, designated "normal," roentgenologic examination of stomach and duodenum was negative.

ages. If we had had such figures we could have corrected the percentages derived from the study of this patient's gastric acidity, and we could then have balanced them against the risk of operation.

Obviously, of course, many a person must refuse to take comfort in the fact that the odds are, let us say, nine to one against his gastric lesion being carcinomatous, because if he should happen to be the one unfortunate man in ten, his life will be forfeit. But, even so, it is a step in advance to secure some figures on which to base what may be, for the patient, the most momentous decision of a lifetime.

## SUMMARY

Using large masses of data collected and analyzed

during the last several years, the writers have attempted to express in figures the probability that a man or woman submitting to gastric analysis at The Mayo Clinic in a given decade of life, with a given gastric acidity, measured one hour after an Ewald type of meal, is suffering with gastric carcinoma, gastric ulcer, duodenal ulcer, or one of a residual group of other diseases or neuroses.

Many interesting and surprising and diagnostically helpful facts have emerged from a study of the material here analyzed.

Obviously the figures published would not be applicable in the case of a patient seen in an office or

## Women

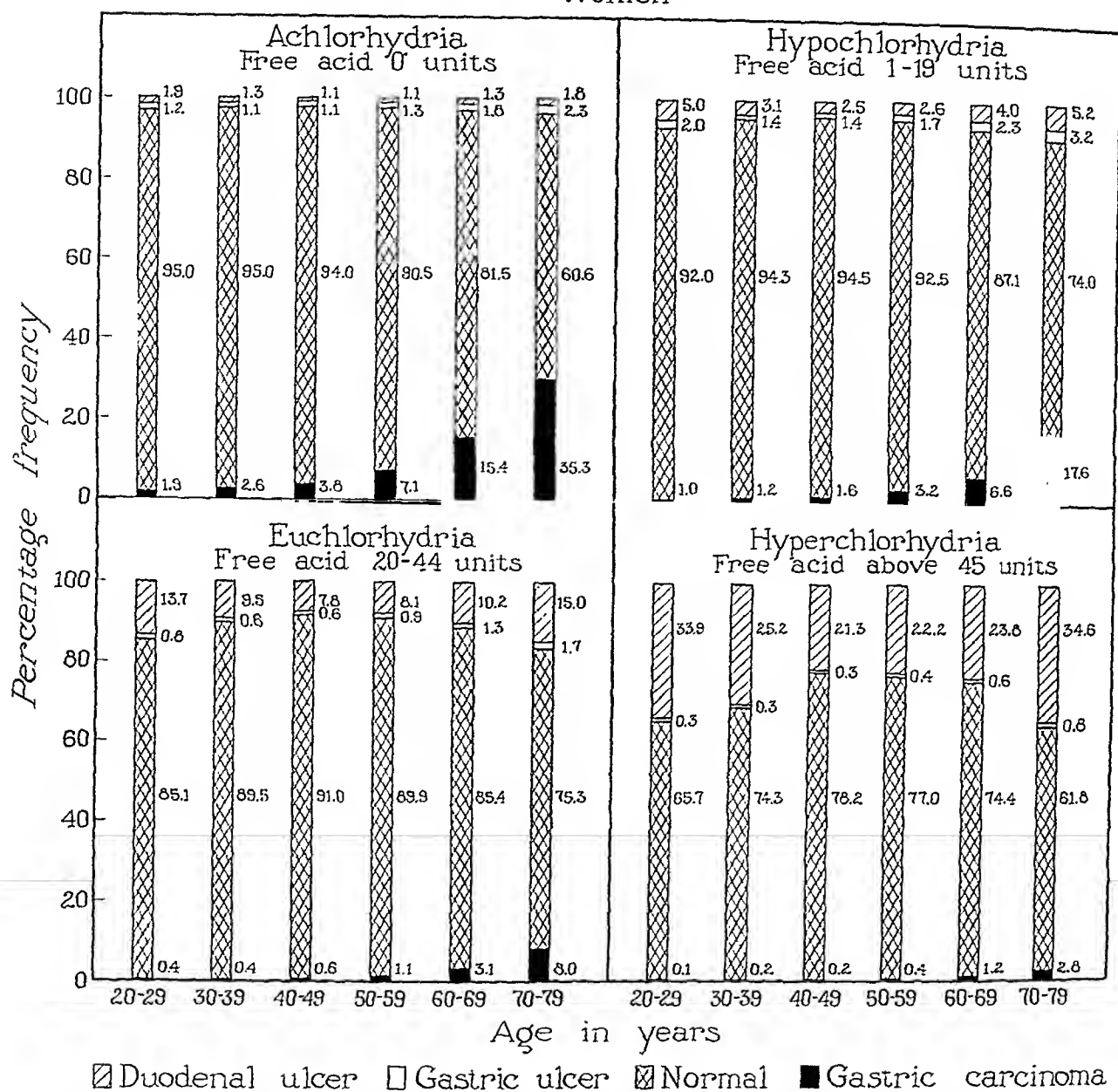


Fig. 1b. Percentage incidence of duodenal ulcer, gastric ulcer, and gastric carcinoma in women of different ages with achlorhydria, hypochlorhydria, eucharhydria, and hyperchlorhydria. In the residual group, designated "normal," roentgenologic examination of stomach and duodenum was negative.

hospital if the composition of the clinical material seen there varied widely from that observed at The Mayo Clinic.

The arithmetic of calculating these probabilities is described for the use of those who may wish to con-

struct their own tables.

It is hoped that a contribution has been made to the methodology of diagnosis; surely the technic here described, or others similar to it, must one day be applied to many other diagnostic problems.

## REFERENCES

1. Alvarez, W. C., and Ascanio, Hugo: The age and sex distributions of patients at The Mayo Clinic. *Human Biol.*, 2:185-198, May, 1930.
2. Comfort, M. W., and Vanzant, Frances R.: Gastric acidity in carcinoma of the stomach. *Am. Jour. Surg.*, 26:447-456, Dec., 1934.
3. MacLagan, N. F.: The test-meal in the diagnosis of gastric disease. *Lancet*, 2:471-475, Sept. 1, 1934.
4. Vanzant, Frances R., and Alvarez, W. C.: What is the value of one gastric analysis? A study of the daily variations in the gastric acidity of two normal persons. *Proc. Staff Meetings of Mayo Clinic*, 6:419-422, July 15, 1931.
5. Vanzant, Frances R.; Berkson, Joseph, and Alvarez, W. C.: Nomograms delineating standards of normal gastric acidity. *Proc. Staff Meetings of Mayo Clinic*, 8:425-429, July 12, 1933.
6. Vanzant, Frances R.; Alvarez, W. C.; Berkson, Joseph, and Eusterman, G. B.: Changes in gastric acidity in peptic ulcer, cholecystitis and other diseases. *Arch. Int. Med.*, 52:616-631, Oct., 1933.
7. Vanzant, Frances R.; Alvarez, W. C.; Eusterman, G. B.; Dunn, H. L., and Berkson, Joseph: The normal range of gastric acidity from youth to old age: an analysis of 3,746 records. *Arch. Int. Med.*, 49:345-359, March, 1932.

## SECTION III—Nutrition

### A Year's Exclusive Meat Diet and Seven Years Later

By

CLARENCE W. LIEB, A.M., M.D.  
NEW YORK CITY, NEW YORK

IN 1926, the writer published the following article: "The Effects of An Exclusive Long-continued Meat Diet," based on the history, experience and clinical survey of Vilhjalmur Stefansson, Arctic Explorer.\*

This paper brought out the following medical facts regarding Stefansson's life in the Arctic.

1. He spent altogether eleven and one-half years within the Arctic Circle.
2. He lived for a number of days, totaling nine years, on an exclusive meat diet.
3. He lived for nine successive months on an exclusive meat diet.
4. He reached his maximum weight while subsisting on meat (fish).
5. His sense of physical and mental well being was at its best during that period of his life.
6. He found that the exclusive meat diet worked as well when he was inactive as when active, and as well in hot weather as in cold.
7. Constipation was never present. One month's entire absence from exercise produced neither constipation nor muscular weakness. (Stefansson avers that not a single case of constipation was observed in 600 exclusively meat-eating Eskimos for a period of three years).
8. His hair thickened, and his scalp became healthier.
9. Tooth decay was apparently much less rapid.

A physical inventory made of Stefansson in 1922 when he was 43 years old, was as follows: Weight—70.8 kg. He was 5 feet 11 inches (180.3 cm.) tall, and well developed and nourished. He looked his years, but no older. The hair was thick and brown with a dry scalp. The face was somewhat asymmetrical. The eyes were normal. The von Graefe, Möbius and Dalmryple signs were not present. The pupils were equal and reacted to light and accommodation. The ears and nose were normal. The tonsils were medium sized and cryptic, with a slight purulent secretion on aspiration. The teeth, objectively, were in good condition, with healthy gums and normal gingival margins. There was no struma. The posterior cervical glands could not be palpated.

The chest measurements were: inhalation, 37 inches (94 cm.); exhalation, 34½ inches (87 cm.): at rest, 35½ inches (90 cm.). A pea-sized cyst was present on the third rib to the right of the sternum. The

lungs were normal throughout to auscultation, palpation and percussion. Fluoroscopy showed peribronchial thickening. The apex beat of the heart was mediad to the left maxillary line; the aortic second beat equaled the pulmonic second; no murmurs were elicited. There was normal response to cardiac functional tests. The pulse was 60, equal, regular, and synchronous. The vessel walls were barely palpable. There was no tremor of the outspread fingers.

The systolic blood pressure was 115 and diastolic, 55, in both arms.

Slight eczema could be seen between the toes, on the right instep and behind the right ear.

The *tache cerebrale* was normal. No dystrophy or cyanosis of the nails was present.

The *crincs* of the abdomen were triangular; the *hirci* were of the female type. No tenderness or masses were felt.

The liver was not felt, nor was the dullness increased. The spleen was not palpable. The gonads were normal.

The knee jerks were active and equal. The Babinski reflex was negative.

Slight external hemorrhoids were present. The prostate was normal. The spine was straight, with free and painless movements.

Men in the various specialties have examined Stefansson, and reports have been entirely negative. Laboratory examinations of the blood (including morphologic, biologic, and chemical) urine, stool, basal metabolism and kidney function tests were normal.

In 1929, the writer published another article with the following title: "The Effects on Human Beings of a Twelve Months' Exclusive Meat Diet,"\* based on intensive clinical and laboratory studies on two Arctic Explorers living under average conditions in a New York climate. This study was made at the Russel Sage Foundation at Bellevue Hospital, under the supervision of the following scientific committee: Dr. Raymond Pearl (Chairman), Dr. E. F. DuBois, Dr. L. J. Henderson, Dr. E. A. Hooton, Dr. Percy Howe, Dr. E. O. Jordan, Dr. C. W. Lieb, Dr. Graham Lusk, Dr. W. C. McCallum, Dr. Walter L. Niles, and Dr. Clark Wisler.

The following is a clinical and laboratory summary of these findings:

**Caloric Intake:** Stefansson averaged about 2,650 calories a day; 2,100 calories consisting of fat and 550

\*Jour. A. M. A., July 3, 1926, Vol. 57.  
Submitted July 3, 1935.

\*Jour. A. M. A., July 6, 1929, Vol. 93, pp. 20-22.

of protein. Andersen averaged about 2,620 calories a day; 2,110 calories consisting of fat and 510 of protein. Carbohydrate in the meat varied between 20 and 50 calories a day.

**Blood Pressure:** Stefansson maintained a blood pressure of 105 systolic and 70 diastolic during the entire course of his diet. Andersen's blood pressure was 140 systolic and 80 diastolic at the beginning of the diet and 120 systolic and 80 diastolic on the completion of the year's diet.

**Vitality:** In neither subject was there a decrease in physical vigor. Both led sedentary lives throughout the experiment. No subjective nor objective signs or symptoms of a decrease in physical vigor were observed. The same holds true of their mental vigor.

**Heat Tolerance:** Andersen affirms that he endured last summer's heat, if anything, better than during former years.

**Appearance:** Both men appeared ruddier at the end of the experiment than at the beginning.

**Hair:** Andersen noted that his hair stopped falling out shortly after the meat diet was started and that the progressive loss has been checked up to date.

**Teeth:** In neither case has there been any deterioration of the teeth. The dentist who has watched these two subjects throughout the experiment noted a greatly increased deposition of tartar on Stefansson's teeth while on the meat diet than formerly. This is interesting in view of the low calcium content of meat. There was also a notable absence of pyorrhea in both subjects.

**Bowels:** Andersen's bowels have remained normal throughout the diet regimen and required practically no catharsis. Stefansson, who has had a tendency to constipation while living in civilized communities, found no increase in this tendency while on the meat diet. An interesting point in this connection is that in both these men the stools were non-odorous and there was no evidence of gaseous distention or flatus at any time. The stools were somewhat below average size and usually were formed.

**Pulse, Temperature and Sleep:** There was no variation from the normal and usual.

**Metabolism:** The basal metabolism of these subjects showed a uniform variation between minus 10 and minus 20 per cent by the Aub-Du Bois standards. There was a slight rise in metabolic rate of 5 per cent during the first month. It is therefore noted that meat diets do not produce any striking elevation of metabolism.

**Weights:** Andersen weighed 60 Kg. at the start. At the end of one month he weighed 58.5 Kg.; at the end of the second month he weighed 60.5 Kg.; at the end of the year's meat diet, 58 Kg.; after recovery from pneumonia 57 Kg., and at this writing, three weeks after recovery from pneumonia, he has regained his original weight.

Stefansson's original weight was 72.5 Kg. At the end of the first month it was 68 Kg.; at the end of the second month it was 69, and at the end of the year's meat diet 69.4 Kg. From April, 1928, to March, 1929, there was no change in weight. Stefansson's concluding weight after the calorimeter studies had been completed was 69.7 Kg.

**Effects on Kidneys:** 1. No albumin, casts or blood was found at any time during the course of the experiment.

2. A "red test" on Andersen showed 55 per cent excretion at the beginning of the experiment; 62 per cent after recovery from pneumonia after completion of a year's meat diet. (The red test was not carried out on Stefansson).

3. Urea clearance showed 100 per cent plus.

These tests would indicate an ability on the part of the kidneys to hyperfunction while on a meat diet.

4. Roentgen examination of the kidneys before and at the conclusion of the meat diet did not show any change in size.

**Mineral Metabolism:** As Aub's work indicated that an acid diet increases calcium excretion and calcium drainage, one would suspect that subjects on a meat diet, which is an acid diet and is likewise low in calcium, would in a year show a calcium deficiency. The increased amount of tartar on Stefansson's teeth and the lack of evidence of lowered blood calcium offers an interesting field for speculation. There was no decreased density in roentgenograms of the hands at the end of the experiment when compared with the hand of a man on a general diet.

**Chemical Analysis of the Blood:** The chemical composition of the blood was little affected except for a slight increase in uric acid and a temporary lipemia. The latter occurred only after unusual amounts of fat were taken. Non-protein nitrogen, urea, uric acid, creatinine, sodium chloride, sugar, carbon dioxide combining power, serum calcium, plasma protein albumin (plasma), globulins, total protein (plasma) albumin: globulin ratio, and cholesterol were studied before the meat diet and after an exclusive meat diet for twelve months, and no noteworthy changes were discovered. Of interest was the fact that the dextrose tolerance test, consisting of the ingestion of 100 Gm. of dextrose, developed in Andersen a typical diabetic curve resulting in the spilling of sugar for the two following days.

**Observations on Intestinal Flora (by Dr. John C. Torrey):** No blood appeared in the fecal specimens and rarely any mucus, the latter occurring once in the case of Andersen and twice in that of Stefansson. The stool reactions were generally definitely acid—between pH 6.0 and 6.8—with an inoffensive, slightly acid odor.

The whole meat diet in both subjects caused a simplification of the intestinal flora with a marked reduction both in types and in total numbers of bacteria. The acidophilus, enterococcus and streptococcus types were practically eliminated. The *B. coli* group increased greatly numerically at first but later decreased and for a time in one subject (Andersen) were largely replaced by *B. proteus*. Hemolytic *B. coli* increased in both during the first one to three weeks, then disappeared. No increase in virulence of colon strains occurred. *B. welchii* at the start was present in both subjects in higher counts than usual for normals, and during the first period a great increase occurred. Later the count fluctuated but was generally high. There were very few putrefactive spore-bearing anaerobes at any time. The diet did not appear to introduce them or encourage their growth.

This meat diet did not cause the development of a putrefactive flora in Stefansson and in Andersen only so far as the late appearance of *B. proteus* (noted first after about one year on the diet).

#### PRESENT CONDITION

The writer has made yearly examinations on Stefansson from 1922 up to the present. It may not be

without some scientific interest to know the health status of Mr. Stefansson at this time.

**Age:** 55 years old. Looks healthy and has aged very little in the past four years.

**Weight:** 84 Kg. compared with 70.8 in 1922 and 72.5 in 1928.

**Head:** No headaches, occasional colds, though mild; sinuses normal.

**Hair:** Thick as in 1922. Iron gray in color. Rarely wears a hat.

**Thyroid:** Negative.

**Teeth:** Dr. Henry S. Dunning reports as follows: (April 16, 1935). "The soft tissues are spongy and the gingival margin has been greatly impaired by an accumulation of calcareous deposits that have been allowed to collect over a period of months. He had a couple of pulpless teeth that I removed, namely the lower left second molar and the upper right first bicuspid that was badly broken down. I feel that the investing tissues of his teeth are fairly good in that he has no bone abscesses."

**Eyes:** No *arcus senilis*. Eye grounds normal. Wears glasses only for reading.

**Ears:** Hearing unchanged, though never very acute.

**Smell:** No change. Never very sensitive.

**Taste:** Normal. Never a gourmet.

#### Cardio-respiratory:

**Heart:** Normal sounds. Pulse 72, equal, regular, synchronous. Oculo-cardiac reflex normal. Negative Erben sign. Good response to exercise. Takes no exercise and walks only when absolutely necessary.

**Blood Pressure:** 120/80.

**Arteries:** Slight radial thickening. (See eye grounds).

**Lungs:** Normal.

#### Genito-urinary:

**Prostate:** Normal.

**Kidneys:** No nycturia. Urine normal in every way.

**Gastro-intestinal:** No gas, heartburn or other stomach symptoms. His diet is poorly balanced. He eats three meals a day, taking a very light breakfast of one egg, bread and coffee. His lunch and dinner are of about an equal consistency. He takes a moderate amount of meat twice a day; vegetables in moderation, cheese once or twice daily, no bread at these meals, usually no deserts, particularly of the starchy kind. He very rarely takes fruit and his milk intake is negligible. He drinks a glass of water at meals and none between meals; two to four cups of coffee daily with cream and sugar and tea occasionally without milk or sugar. He has no digestive symptoms either chronic

or acute. His bowels move every other day very regularly with the occasional use of mineral oil. He has had two attacks of "food poisoning" during the past two years. Stool examination recently showed normal reaction and food residue, no mucus and practically normal bacteriological findings.

**Liver:** Dullness normal limits. Not palpable. No tenderness over gall bladder. (Typhoid in Arctic).

**Appendix:** No tenderness or spasm in right lower quadrant. No cecal splash.

**Rectum:** Small internal hemorrhoids, sphincter normal.

**Proctoscopic Examination:** Negative.

#### Neuro-muscular:

**General Neurological tests:** Elicit normal results. No insomnia.

**Joints and muscles and feet:** Normal.

#### Blood Chemistry:

|                                       |        |
|---------------------------------------|--------|
| Blood cell volume .....               | 45     |
| Plasma urea .....                     | 28.5   |
| Plasma chlorides .....                | 640    |
| Whole blood sugar .....               | 98     |
| Plasma creatinin .....                | 1.4    |
| Whole blood uric acid .....           | 4.4    |
| Carbon dioxide absorption capacity... | 60     |
| Plasma icterus index .....            | 10.0   |
| Serum calcium .....                   | 9.9    |
| Sedimentation rate .....              | normal |

#### Blood Count:

|                         |            |
|-------------------------|------------|
| Leucocytes .....        | 5, 780     |
| Erythrocytes .....      | 5, 100 000 |
| Hemoglobin .....        | 102        |
| Color index .....       | 1.0        |
| Blood cell volume ..... | 48         |
| Saturation index .....  | 1.02       |
| Volume index .....      | .98        |

#### Stool examination:

Normal color, odor, consistency. No mucus. Slight reaction for occult blood (hemorrhoidal origin), normal microscopic findings. H-ion conc. pH 6.9. Bacteriological studies showed a high count of normal strains of *B. coli*; many *enterococci* (non-toxic organisms) and a high count of *Strep. viridans* (alpha) of moderate toxicity.

**Basal Metabolism:** Minus 8.

Mr. Stefansson has been in excellent general health since his exclusive meat diet. He has led a very sedentary life and has worked fairly strenuously at writing, lecturing and in a consulting capacity with an aviation company.

## ABSTRACTS

GILDEA, M. C. L.; CASTLE, W. B.;  
GILDEA, E. F., AND COBB, S.

*Neuropathology of Experimental Vitamin Deficiency. Amer. Jour. Path., XI, 65, p. 669, July, 1935.*

The authors report further studies on the attempt to produce experimental lesions of the spinal cord by means of diets deficient in vitamin B complex in the hope of showing a relationship to those types of combined system disease seen in pernicious anemia, pellagra, and chronic alcoholism.

Four series of dogs were used in these experiments. All were placed upon a basal diet deficient in vitamin B complex. Dogs kept upon this diet, and without treatment with vitamin B concentrates, developed early signs of acute disturbance of the central nervous system and soon died. Only minimal histological changes were found in the central nervous system in these animals. In other dogs repeated treatments with vitamin B concentrates were used to prolong their lives. They developed

gradually a degree of spastic ataxia and eventually motor paralysis. Definite histological lesions of the central nervous system were found in all but one animal of the series. Degenerative changes were noted in the cerebral and Purkinje cells and in the cells of the anterior horns in seven dogs. Myelin degeneration in the spinal cords were also observed and in three animals changes in the peripheral nerves were present.

N. W. Jones, Portland.

## SECTION V—*Therapeutics*

### Gastro-Intestinal Diets \*

#### HYPER-NUTRITION DIET

##### *Breakfast*

Fruit—Orange, grapefruit, baked apple or any stewed fruit, prunes in particular.

Cereal—Any cooked cereal with three ounces of cream (oatmeal at least twice a week).

Eggs—Any form except fried, with bacon. May substitute mutton or lamb chop broiled.

Bread—Two pieces of bread or toast with an abundance of butter.

Beverage—Milk, weak tea, cocoa, coffee.

##### *Mid-Morning*

Six ounces of equal parts of milk and cream.

##### *Noon Meal*

Soup—Puree of pea, bean, potato or celery or oyster stew.

Meat—Choice of chipped beef with cream; baked tomato with cream, chicken, cheese or tongue sandwich.

Vegetables—Choice of one vegetable as desired.

Bread—Abundance of bread and butter, whole wheat preferable.

Dessert—Choice of dessert given below.

##### *Mid-Afternoon*

Same as mid-morning or egg and milk and malted milk.

##### *Evening Meal*

Soup—Puree of pea, bean, potato, celery, bouillon, chicken broth with rice, noodles.

Meat—Roast beef, tenderloin, brains, sweetbreads, boiled; lamb or mutton chop; fowl or fresh fish.

Vegetables—All vegetables are allowed. Choose one green and one starchy vegetable.

Salad—Lettuce and tomato. Olive oil and mayonnaise dressing.

Bread—Two pieces of bread and lots of butter.

Dessert—Apple, lemon, peach custard or cream pie; bread, chocolate, rice, tapioca or cornstarch puddings; custard, blanc mange, egg souffle, floating island, ice cream, spanish cream, plain cake or any stewed fruit.

Almonds, pecan nuts, walnuts, dates, raisins, molasses.

Beverage—Same as Breakfast.

##### *9:30 P. M.*

Same as mid-afternoon with crackers and butter.

Avoid tea and coffee except as above, salads except as directed, raw fruits, coarse vegetables, candy, pork,

thin soup, hash, cabbage, scrapple, veal and fried foods or any food highly seasoned.

#### CAUTIONS

ARISE ONE HOUR BEFORE BREAKFAST AND TAKE A BRISK WALK.

TAKE A COLD SPONGE BATH EACH MORNING.

TAKE MEALS AT THE SAME HOUR EACH DAY.

RETIRE AND ARISE AT THE SAME HOUR.

TAKE A MODERATE AMOUNT OF OUTDOOR EXERCISE.

TAKE AT LEAST ONE QUARTER POUND OF BUTTER DAILY.

#### ACHYLIA—SUBACIDITY

##### *Breakfast*

Fruit—Juice of orange, prunes, or grapefruit.

Cereal—Any cooked cereal with cream and sugar.

Eggs—One soft boiled egg.

Bread—Toast or stale bread with butter.

Beverage—Cup of cocoa or weak tea with milk.

##### *Dinner*

Soup—Bouillon, broth or puree of vegetables.

Vegetables—Select two of the following vegetables: baked, mashed or creamed potatoes, macaroni, or spaghetti, asparagus, or spinach (small quantity) or rice, tapioca, hominy, peas, or beans (mashed and strained).

Meat—Boiled or broiled calves brains or sweetbreads; fresh fish, lamb, or chicken finely divided.

Dessert—Jello or simple desserts.

Bread—Toast and butter.

##### *Supper*

Meat or Substitute—Two eggs, any form except fried, raw or stewed oysters, cream or cottage cheese.

Vegetables—Choice of vegetables as above or cooked cereal.

Bread—Bread (white) with butter.

Dessert—Stewed peaches or apricots, baked apple without skin, fruit juice, plain cake, simple pudding or custard.

Beverage—Cocoa or weak tea.

#### CAUTIONS

AVOID ALL UNCOOKED FOOD, ALL HEAVY FIBROUS FOOD, AS CABBAGE, TOMATO, CORN, CELERY, SALADS, PICKLES, RELISH, ETC.

CHEW FOOD THOROUGHLY.

DINNER MAY BE TAKEN IN THE EVENING IF DESIRED.

\*From the Diet Manual of the Mount Sinai Hospital, Philadelphia. Through the Courtesy of Miss J. Marie Melgaard, Director, Dietary Department.



## SECTION VI—*Abdominal Surgery*

### Gastro-Intestinal Manifestations Accompanying Diseases in the Upper Urinary Tract\*

By

BENJAMIN S. ABESHOUSE, Ph.B., M.D.†  
BALTIMORE, MARYLAND

#### INTRODUCTION

IN this era of instrumental diagnostic precision and highly specialized roentgenographic technique there is a tendency on the part of clinicians and urologists alike to pay but little attention to a careful analysis of the symptoms of urinary diseases. It is not entirely amiss to point out that, now as in the past, an accurate diagnosis of any urinary disorder must be based on a complete history, careful general examination together with a detailed and thorough urological examination. Unfortunately, in the evaluation of the symptoms of any urinary disease, there is a tendency to minimize or overlook symptoms referable to any other organ or system of organs outside of the urinary tract. To facilitate the establishment of an early and correct diagnosis, it is imperative to study carefully the symptomatology of any urinary disease in the light of the body as a whole.

Gastro-intestinal manifestations are by no means uncommon occurrences in diseases of the upper urinary tract. Practically every case is accompanied by some gastro-intestinal complaint of a transitory or permanent character, *i.e.*, nausea, vomiting, epigastric distress, abdominal discomfort, constipation, diarrhea, etc., which is readily forgotten by the patient and glibly dismissed as of no importance by the physician. In most of the older textbooks of urology, there is scant or no reference to the occurrence of gastro-intestinal symptoms of genito-urinary disease. The more recent textbooks discuss the subject at no great length and lay particular stress on their association with movable kidney.

The gastro-intestinal symptoms may be classified as (a) *toxic*, (b) *mechanical*, or (c) *reflex*. The toxic type may be the manifestations of an uremic or infectious process in the kidney. The frequent occurrence of nausea and vomiting in an acute or chronic infection of the upper urinary tract, *i.e.*, nephritis, pyelitis, pyelonephritis, tuberculosis, may be due to the reaction to bacterial toxins or to excessive nitrogenous compounds in the blood. The latter is associated with a

failing renal function and is indicated by a high non-protein nitrogen in the blood.

Friedenwald and Morrison maintain that in the early stages of the various nephritides the amount of toxic substances accumulating in the blood is slight and, being excreted in small amounts in the gastro-intestinal tract, gives rise to minor digestive disturbances. As the disease process in the kidneys progresses and the amount of toxic products in the blood increases, these toxic substances are excreted into the gastro-intestinal tract in excessive amounts and give rise to grave digestive disturbances as a result of the development of a gastro-enteritis or ulceration.

At other times, the gastro-intestinal symptoms are obstructive in character and are due to the pressure of enlarged kidney or renal tumor or to the irritation produced by an accumulation of blood, pus or urine in the perirenal space upon the peritoneum and intestines overlying the ureter, kidney and perirenal tissues. However, in the majority of cases, the gastro-intestinal symptoms are due to the reflex action of the stomach or intestinal tract to stimuli originating in the upper urinary tract and are unassociated with any disease of intestinal origin. Symptoms pointing to a difficulty in urination may be entirely absent and the urine may be normal. Tixier and Clavel have called this phenomenon of stimulation of the entire gastro-intestinal tract or a specific portion thereof by nerve impulses originating in the retroperitoneal area, *i.e.*, ureter, kidney or perirenal space "the retroperitoneal syndrome."

Every surgeon of wide experience has encountered patients who were suffering from primary disease of the upper urinary tract and presented acute or chronic gastro-intestinal symptoms which have been mistaken for a gastro-duodenal, hepatic, appendiceal or colonic lesion and have been so confusing as to cause unnecessary surgical intervention. To the surgeon's extreme disappointment, operation disclosed a normal appendix, stomach, duodenum, gall bladder and pelvic organs with an absence of fluid or pus, although the bowel may be dilated in some areas and contracted in others. Immediately following the operation, the intestinal spasm or distension disappears and the patient recovers. Some days or weeks later the patient has another similar attack which is quite confusing until an urolo-

\*From Urological Service, Sinai Hospital, Baltimore, Maryland.  
†Attending Urologist, Sinai Hospital. Instructor in Genito-urinary Pathology, Univ. of Maryland Medical School.  
Read at the meeting of the Baltimore-Washington branch of the American Urological Association in Baltimore, Md., on January 18th, 1935.  
Submitted April 26, 1935.

gical investigation is ordered and the true nature of the underlying urinary disease is revealed.

The importance and necessity of a thorough pre-operative, urological examination in cases with obscure abdominal pain or uncertain diagnoses is clearly established by the statistical studies of the condition of patients before and after major abdominal operations. Connor reported that 10 per cent of all the cases admitted to the Mayo Clinic required urological study. Stevens maintained that urological investigation was indicated in at least one-third of all patients entering a hospital with uncertain diagnoses. Reports from other large clinics revealed that 15 to 20 per cent of patients with renal or ureteral lesions had been previously subjected to abdominal operations for the same complaint. Blesh reviewed 5000 surgical cases in many of which the appendix was removed and found that 40 per cent of the patients complained of the same symptoms after as before the operation. Liek analyzed 1000 cases of chronic appendicitis subjected to operation and observed only 100 cases of genuine chronic appendicitis. Lowsley and Twinem studied 84 urological cases and noted that 39 patients had previously undergone some major surgical operation without relief of symptoms. In this latter group, 31 had the appendix removed.

Beck analyzed 284 private patients with urologic disease examined by Goldstein and Abeshouse and found that 151 patients (57 per cent) suffered from gastro-intestinal symptoms and in 85 patients it was the chief complaint. In this series 207 operations had been performed prior to the urological study. In 137 cases, operation was performed on the abdominal organs which included 58 appendectomies with no relief in 31 cases, 48 pelvic operations with no relief in 26 cases, 9 gall bladder operations with no relief in 2 cases, 2 operations for gastric ulcer with no relief in one case, and 6 exploratory laparotomies with no relief in any case. In a review of 300 cases of urinary tract disease, Cecil found that pain was present in 183 cases and was limited to the abdomen in over 22 per cent. There were 67 cases of stone in the kidney or ureter of which 19 cases (28 per cent) presented abdominal pain and in over 20 per cent the pain was so misleading as to lead to abdominal operation.

#### HISTORICAL BACKGROUND

The present conception of the "retroperitoneal syndrome" is based on the correlation of clinical observations and experimental data. In 1897, Tixier observed that irritation of the parietal peritoneum initiated a series of reflexes culminating in a condition which he described as "abdominal shock" or "peritonism." Later it became apparent from numerous clinical observations that similar reflexes might originate in the kidney and perirenal tissues. In 1929, Clavel presented a comprehensive review of the various surgical affection of the kidney, *i.e.*, tuberculosis, neoplasm, polycystic disease, pyonephrosis, etc., which were accompanied by peritoneal or gastro-intestinal syndromes with no urinary symptoms. Sternberg, Stewart, Quenu and others have reported cases of renal lithiasis which produced severe abdominal and peritoneal phenomena suggesting ileus. Marie, Samuels and Kern, McGlannon, Alle-

man and others have described cases of congenital and acquired hydronephrosis in which gastro-intestinal symptoms were the most prominent manifestation of the renal disease. Any ureteral or renal lesion which is accompanied by an accumulation of urine, pus or blood in the periureteral or perirenal space causing an irritation of the posterior parietal peritoneum may simulate an intestinal obstruction or peritonitis. Such phenomena have been observed following perinephritic abscess (Tixier, Higgins, Berkman), spontaneous perirenal hemorrhage (Greco, Grasman), traumatic rupture of the kidney with retroperitoneal effusion of hemorrhage (Tixier, Eisenklam), and extra-peritoneal rupture of a hydronephrosis (Von Saar). Recently the Author reviewed 64 cases of rupture of the renal pelvis and observed that gastro-intestinal manifestations were a constant feature in every case and occasionally were the predominant manifestations.

#### THE NERVOUS MECHANISM INVOLVED IN THE RETROPERITONEAL SYNDROME

A knowledge of the anatomy and physiology of the upper urinary and gastro-intestinal tracts is essential to explain the symptoms of reflex origin which constitute the retroperitoneal syndrome.

The nerve supply of the kidney has been studied by Papin, Petit-Dutailis, Nisio, Labat and others. The twelfth dorsal and first lumbar segments of the spinal cord serve as the source of the renal nerve supply. The visceral nerves of the kidneys are derived from the renal plexus on each side. The latter plexus originates from the inferior portion of the coeliac (solar) plexus especially from the corresponding aortic-renal ganglion which receives (a) the posterior renal nerve or the third splanchnic, derived from the twelfth thoracic ganglion, (b) some fibers from the lesser splanchnic

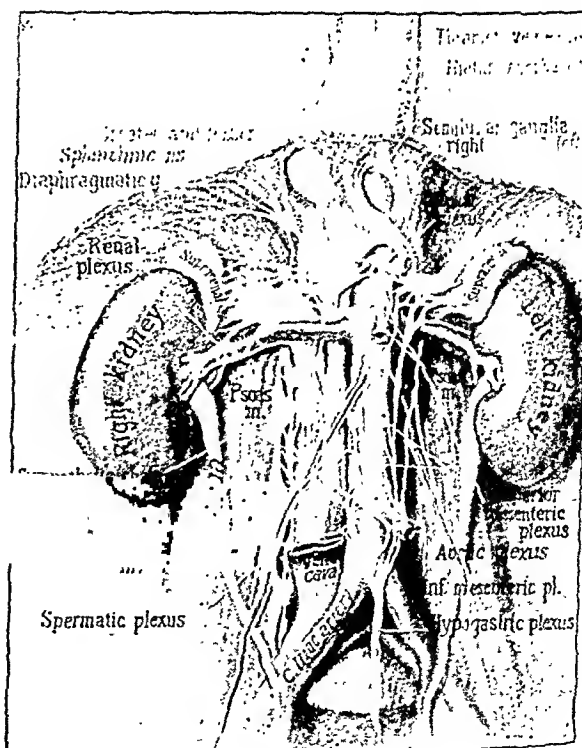


Fig. 1. The solar plexus and the nerve supply of the kidneys. (After Labat: Regional Anesthesia).

Fig. 1

nerve and (c) a branch from the first lumbar sympathetic ganglion (Fig. 1). The kidney also receives communications from the vagus nerve whose fibers terminate in the coeliac plexus. The renal nerves form a network, which consists of numerous small parallel longitudinal fibers with transverse anastomoses and surrounds the renal artery. These small fibers follow the renal artery and all its branches into the renal parenchyma to reach the Malpighian corpuscles, Bowman's capsule, tubular epithelium and interstitial tissue. Nerve terminations have also been demonstrated in the smooth musculature of the pelvis, in the renal capsule and in middle layer and adventitia of the blood vessels of the kidney.

Wharton has recently made a detailed study of the innervation of the ureter which confirms some of the observations of the early investigators and further enhances our knowledge of this subject. According to Wharton, the ureter receives a nerve supply which is independent of the innervation of the kidney and the bladder. The efferent nerves of the ureter are derived from (1) the lowest renal ganglion at the upper end of the spermatic plexus and (2) the abdominal sympathetics (aortic, hypogastric and pelvic plexuses) which constitute the coeliac plexus. The aortic plexus receives branches from the upper lumbar sympathetic (prevertebral) ganglia and the pelvic plexus receives direct fibers from the sacral cord. The posterior peritoneum in the region of the kidney and ureter is innervated by the same nerves supplying these organs. Anatomical dissections reveal many anastomoses between the renal plexuses and the superior and inferior mesenteric plexuses.

The innervation of the stomach, small intestines, cecum and transverse colon is derived in part from the same source as the kidney and ureter. These alimentary organs receive their nerve supply from (1) the vagus nerve which contains parasympathetic (excitomotor) fibers, and (2) coeliac plexus whose sympathetic (inhibito-motor) nerves come by way of the greater splanchnic nerve from the fifth to the ninth dorsal segments of the cord and through the lesser splanchnic from the tenth to the twelfth dorsal spinal segments (Fig. 1). The remainder of the gastro-intestinal tract (descending colon, sigmoid, rectum and anal sphincter) and the lower genito-urinary tract have a common nerve supply consisting of (a) sympathetic (inhibito-motor) fibers derived from the lumbar segments of the cord and (b) parasympathetic (excitomotor) fibers originating in the second, third and fourth sacral segments. The physiological response to stimulation of these various nerves has been accurately determined. Stimulation of the vagus nerve results in an initial inhibition of the gastric and intestinal movements of very short duration followed by an increase in intestinal motility (hyperperistalsis). Stimulation of the sympathetic nerves is followed by a decrease in the intestinal movements. The effect of stimulation of the sympathetic or parasympathetic fibers upon the vari-

ous sphincters in the gastro-intestinal tract is usually opposite to that effect upon the intestinal walls.

### PHYSIOLOGICAL RESPONSE TO STIMULI ORIGINATING IN UPPER URINARY TRACT

Inasmuch as the upper urinary and gastro-intestinal tracts are innervated by sympathetic and parasympathetic nerves and one of the chief functions of the vegetative nervous system is to insure proper coordination of the various organs of the body, it is reasonable to suppose that any disturbance or dysfunction in one organ may give rise to symptoms in other organs possessing a similar innervation. Such phenomena have been recognized for a long time and have been described as "viscero-visceral reflexes" by Sir James MacKenzie. He explained the production of pain through visceromotor reflexes which occurs when stimuli from an affected organ, if of adequate strength, stimulate other nerve cells of the spinal cord in the neighborhood of those from the affected viscus. The response to such stimuli varies according to the intra- and inter-segmental connections of the efferent nerves and the particular function of the afferent nerves reflexly stimulated. A familiar example of this mechanism is the spasm of the gastric and intestinal musculature resulting in nausea and vomiting associated with an acutely inflamed appendix.

The same mechanism may suffice to explain the occurrence of referred gastro-intestinal symptoms in diseases of the upper urinary tract. The coeliac plexus appears to be the center of reflex action for stimuli originating in the kidney, ureter or posterior parietal peritoneum. Some of these reflexes may take a short circuit as they pass through the renal ganglia and the inferior mesenteric ganglia and are referred to the visceral branches supplying the various portions of the gastro-intestinal tract (Fig. 2). Other reflexes undoubtedly have a longer circuit as impulses from the kidney and perirenal area reach the spinal cord and

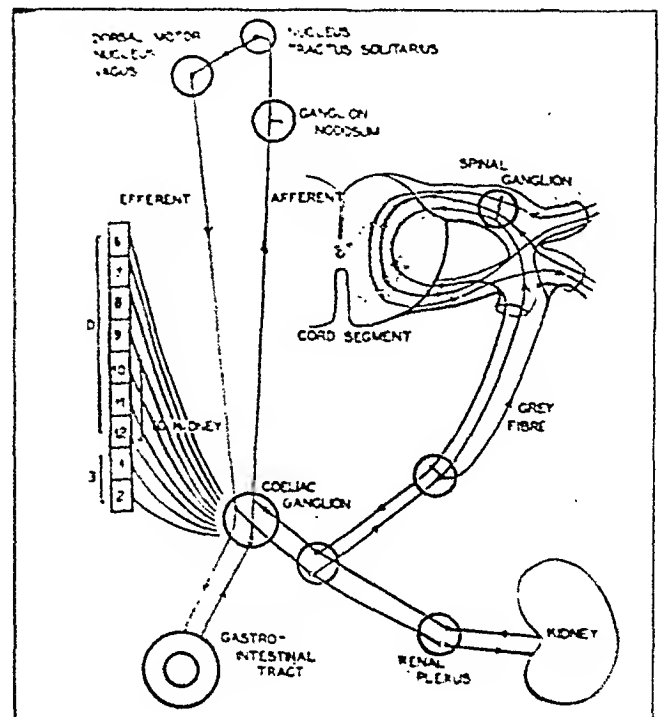


Fig. 2. Diagram showing the afferent and efferent routes of renal stimuli. The centrifugal route of the various renodigestive, visceromotor and viscerosensory reflexes can be readily determined. (After Smith: Canadian Med. Ass. J., 1933; 28:281).

pass upward in the tractus solitarius to the nucleus of the vagus. From this point these impulses are further transmitted through parasympathetic fibers which are distributed to the stomach and upper intestines causing a transitory arrest of gastric and intestinal motility followed by an increase in motility. This interference with the musculature of the stomach and duodenum may produce any of the usual symptoms of dyspepsia, *i.e.*, pain, nausea, vomiting, heartburn, belching, epigastric fullness, etc. By similar reflex connections through the intermedio-lateral column cells of the spinal cord, impulses pass through the sympathetic (inhibito-motor) fibers supplying the large bowel resulting in abdominal pain, cramps, constipation, diarrhea or ileus.

Stimuli originating in the upper urinary tract not only cause reno-digestive reflexes but also are projected in the various skin zones producing referred pain. Head has studied the topography and mechanism of pain projection on the wall of the abdomen in renal colic and other diseases of the kidney. The pain usually is associated with localized muscle spasm or rigidity and cutaneous hyperesthesia which may simulate the findings associated with an acute abdominal lesion. It is also well to point out that other general symptoms, *i.e.*, changes in pulse, respiration and blood pressure, vasomotor disturbances, etc., may accompany many of the reno-digestive reflexes as a result of stimulation of the parasympathetic and sympathetic nerves which act as the centrifugal route of the reno-digestive reflexes.

There is much experimental evidence to support the above data and to confirm the clinical observations that stimuli originating in the kidney or perinephritic tissues may produce motor or inhibitory reflexes in the gastro-intestinal tract. Tixier and Clavel studied the influence of renal and perirenal stimuli on gastro-intestinal motility and observed increased contractibility of the stomach and the intestines when the kidney parenchyma, pelvis and parietal peritoneum were stimulated. They also studied the effect of an injection of salt solution in the retroperitoneal area of guinea pigs and found some intestinal segments dilated and congested as though affected by vasodilatation and paralysis while the intermediate segments appeared pale and contracted. Carnot and Thomas and Wheelan showed that spasm of the pylorus could be caused by stimulation of almost any visceral efferent nerve. The same phenomenon could be induced by rubbing, stretching or crushing the urinary bladder, ureter, kidneys, intestines, parietal peritoneum and anal sphincters. The same effects were also obtained by section of the vagi in the neck.

From a physiological viewpoint, the reno-digestive reflexes concerned in the retroperitoneal syndrome may be classified according to their effects upon the various portions of the gastro-intestinal tract. The principal types are the (a) reno-gastric, (b) reno-intestinal, (c) reno-hepatic and (d) reno-peritoneal. The first two types are by far the most important. The reno-gastric reflexes may be motor, secretory or vasomotor in character and their effect is either a stimulation or inhibition of gastric secretion and motility. These stimuli may affect either the stomach or duodenum or both; the pylorus is particularly susceptible to such stimuli. The reno-intestinal reflexes are also motor, secretory or vasomotor and may produce either

spastic contractions or paralysis of the intestinal musculature. The majority of reno-intestinal reflexes of renal or perirenal origin affect the large intestines, particularly the cecum and colon; those of right ureteral origin may produce similar phenomena in the cecum and appendix and those of left ureteral origin appear to affect the descending colon, sigmoid and rectum. The various types of reno-intestinal reflexes may be associated with each other or combined with reno-gastric or cardiac, respiratory or vasomotor reflexes causing a group of symptoms simulating peritonitis or intestinal obstruction.

#### THE ORIGIN OF STIMULI WITHIN THE UPPER URINARY TRACT

The point of origin of the reno-digestive reflexes varies in the different clinical cases. The majority of the lesions in the upper urinary tract which initiate the reflex stimulation of the gastro-intestinal tract can readily be diagnosed by a thorough urological study including a pyelographic study of both ureters and pelvis in the horizontal and upright positions. In a few cases the exact nature of the underlying renal lesion can only be determined at operation. The following indicate the more common sites and lesions which serve as the starting point for the various reno-digestive reflexes:

(a) Stimulation of the mucous membrane of the renal pelvis or ureter by a stone, pus or blood clot, *i.e.*, renal or ureteral calculi, pyelitis, pyelonephritis, intrarenal hemorrhage following trauma, tumor, etc.

(b) Stimulation of the nerve endings in the pelvis or ureter as a result of distension (hydronephrosis or hydroureter) secondary to any intrinsic or extrinsic obstruction of the ureter or pelvis, *i.e.*, congenital or acquired stricture of ureter; aberrant vessels or adhesions crossing the ureter or at the ureteropelvic junction; pressure of an extraurinary tumor upon the ureter, etc.

(c) Stimulation of the nerve endings in the renal parenchyma or capsule by an inflammatory or neoplastic disease process, *i.e.*, pyelonephritis, cortical abscess, renal carbuncle, pyonephrosis, tuberculosis, tumors, solitary cyst, polycystic disease, etc. The response to such stimuli is greater when the disease process is located in the cortex or immediately adjacent thereto.

(d) Stimulation of the fibers of the renal plexus and indirectly of the coeliac plexus as the result of the traction exerted on the renal pedicle and fat capsule of the kidney by a congenital or acquired dystopic kidney, *i.e.*, movable kidney, congenital anomalies of the kidney, etc.

(e) Stimulation of the fibers of the renal and coeliac plexuses as a result of distension, irritation or laceration of the nerve fibers in the perirenal tissues and posterior parietal peritoneum produced by any subcapsular or perirenal collection of urine, pus or blood, *i.e.*, perinephritic abscess, perinephritis, rupture of the kidney with intrarenal, subcapsular or perirenal hemorrhage or extravasation of urine, hemorrhage within a tumor or cyst, etc.

(f) Stimulation of the nerve endings in the posterior peritoneum and the adjacent intra-abdominal organs as a result of the pressure or traction exerted upon these structures by any intrarenal or extrarenal swelling of an obstructive, inflammatory, hemorrhagic

or neoplastic character, *i.e.*, renal tumor, cyst, pyonephrosis, perirenal hemorrhage or abscess.

The response to these stimuli may vary in the same or different individuals. In the majority of instances, the centrifugal route of the above stimuli most often results in the projection of pain in the various skin zones. In only a small percentage of the cases, the response to these stimuli is manifested by reno-digestive reflexes. According to Tixier and Clavel there are several factors which exert a considerable influence upon the development of these reno-digestive reflexes, *viz.*, (1) summation of primary irritative stimuli; (2) sensitization of the nerve centers; and (3) individual predisposition.

1. *Summation of primary irritative stimuli:* The mechanism responsible for the production of reno-digestive reflexes is a complex one. Clinical and experimental studies show that a solitary or isolated renal stimulus is not always sufficient to produce a reflex reaction but that the latter readily follows a summation of different stimuli caused by the same or a co-existing lesion. For example, a large calculus, situated in the renal pelvis and unaccompanied by distention or infection may evoke no greater response than localized pain whereas a small stone totally occluding a ureter and accompanied by dilatation of the ureter and pelvis and by irritation of the ureteral mucosa may produce a more complex response. For the same reason cortical lesions, unless accompanied by a slight traction on the pedicle, distention of the pelvis or irritation of the perinephritic tissue or posterior peritoneum, are not likely to cause reno-digestive reflexes.

2. *Sensitization of nerve centers by chemical or bacterial toxins:* Experimental studies have shown that pilocarpine increases the intensity of reno-digestive reflexes and lowers the threshold of stimulation necessary to initiate these reflexes whereas atropine and nicotine have an opposite effect. It is highly probable that a similar sensitization of the nerve centers occurs in some of the clinical cases. Some nitrogenous compound found in the blood of uremic patients or some chemical or bacterial toxin associated with an infectious process in the urinary or gastro-intestinal tract could well serve as sensitizing agents.

3. *Individual predisposition:* It is a well established fact that certain individuals respond differently to similar stimulations. Some investigators attribute this to nervousness, emotional instability, auto-intoxication, lowered resistance, etc., while others have suggested an imbalance in the vegetative nervous system, *i.e.*, vagotonia or sympathicotonia as a predisposing factor. The occurrence of an inherent tendency or predisposition to reno-digestive reflexes is substantiated by various case reports in which the like or different gastro-intestinal syndromes have recurred in the same individual following repeated attacks or episodes of a disease in the kidney or ureter. (Case VIII).

### SYMPTOMATOLOGY

Clinically the gastro-intestinal manifestations of these reno-digestive reflexes may be classified as (1) gastro-duodenal, (2) biliary, (3) appendiceal, (4) colonic, and (5) peritoneal. Urinary symptoms are usually present together with the gastro-intestinal phenomena although occasionally there are no symptoms pointing to a primary disease in the upper urinary tract and the urine is negative.

(1) *Gastro-duodenal (dyspeptic) type:* The predominant symptoms of this group are nausea and vomiting which may be associated with any disease of the upper urinary tract. It is almost constantly associated with ureteral or renal colic. Less frequently, epigastric pain or discomfort, belching or heartburn may be present. Not infrequently these symptoms follow dietary indiscretion and a diagnosis of acute indigestion is made. Although these symptoms are not typical of gastric or duodenal ulcer, such a diagnosis is often made and the usual therapeutic measures are tried with no success (Case I). The urological origin of these symptoms is disclosed when a complete diagnostic study including cystoscopy and pyelography is undertaken. After the correct diagnosis has been established, careful questioning will reveal some urological symptom or complaint that has been overlooked or minimized by the patient or physician or both.

Another gastric reflex manifestation of diseases of the kidney and ureters especially following operations on these organs, is acute dilatation of the stomach. In 1903 Laffer reviewed 217 cases of acute dilatation of the stomach and found that 11 cases occurred after operations on the kidney. Stoccarda recently reported a similar case occurring after nephropexy. This syndrome is usually mild and responds quickly to gastric lavage. Aerophagy may also be associated with acute dilatations of the stomach.

In 1910 Aglave reported the occurrence of symptoms of duodenal compression accompanying diseases of the kidney, particularly nephroptosis, and also following nephrectomy. From anatomical studies he concluded that the kidney in its descent pulled the colonic flexure and its mesentery with it and exerted the same traction on the mesenteric artery causing a compression of the duodenum. He also pointed out that the symptoms of chronic duodenal compression are relieved when the patient is put in the knee chest or Trendelenberg position. Cases of chronic duodenal disease due to a large right hydronephrosis, which were completely relieved by operation, have been reported by Colby, Fagge and Smith. Ozeki recently reported a case of duodenal stenosis due to compression of the mesenteric artery occurring after pyelolithotomy.

Bumpus and Thompson reviewed 1001 cases of ureteral calculi and found the pain to be entirely epigastric in 162 cases. In this latter group a diagnosis of peptic ulcer was made in 17 cases and of cholecystitis in the remainder. Zallocco recently reported a case of renal calculi with gastralgie syndrome. Swan reported a case with gastro-duodenal symptoms due to a left renal tumor and demonstrated metastases around the sympathetic nerves (coeliac plexus) having renal and gastric associations.

*Case I:* J. H. C., 50 years, male, car repairman was referred by Drs. Friedenwald and Morrison. This patient was first seen on September 1, 1934. He stated that 18 years ago he had a sharp attack of pain in the left lower quadrant which lasted several hours and required morphine for relief. The pain was accompanied by nausea but no vomiting, chills or fever. There were no urinary symptoms. Since then he has had several attacks of similar pain at intervals of one to two months but for the past year the pain has been present continuously. The pain varied from a dull gnawing to a sharp sticking sensation and did not radiate to the groin or kidney. Occasionally, the pain appeared to be referred to the epigastric region. In the past year, he has complained of marked epigastric



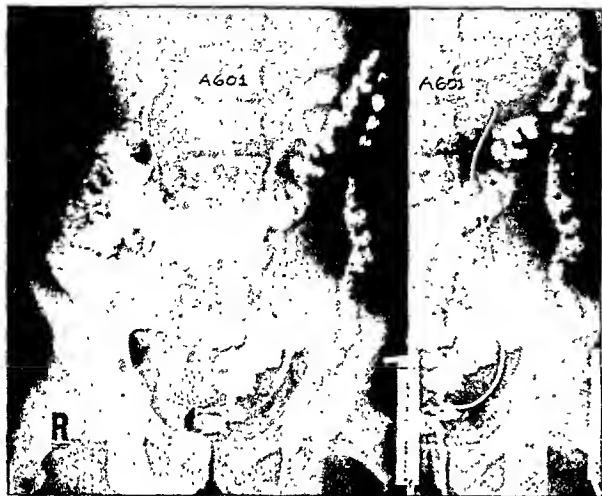


Fig. 3

distress, nausea, belching, heartburn, fullness after eating, and, occasionally, pain after eating. He has lost 11 pounds in the past 2 months. At no time has he had any urinary complaint. He had consulted several physicians in his home town (Keyser, W. Va.) who diagnosed the condition as "dyspepsia," and, in one instance, as gastric ulcer. He was given the usual alkaline medications and put on a modified Sippy diet for 3 months with no relief. He came to Baltimore to consult a gastro-enterologist.

On examination, the positive findings were moderate tenderness in the lower left quadrant and just below the level of the umbilicus and a palpable mass in the left upper quadrant which was slightly tender. The urine contained 8 to 10 p.e. and 2 to 3 r.b.c. per h.p.f. He was sent to a roentgenologist for a gastro-intestinal study and in one of the films a shadow was observed in the left renal area. He was then referred for urological study which revealed a large triangular calculus (2 cm. x 1.5 cm.) in the pelvis of the left kidney (Fig. 3). Pyelogram of the left kidney revealed a marked dilatation of the pelvic and calyces (pyonephrosis). Operation was advised but the patient returned to his home. Several months later, we learned that the kidney was removed by a urologist in a nearby city and the symptoms have disappeared entirely.

**Comment:** This case illustrates the association of gastro-duodenal symptoms with a calculus in the kidney. The patient had been subjected to numerous examinations and various types of treatment for so-called "dyspepsia" and gastric ulcer. The value of a plain plate as a routine preliminary measure in every gastro-intestinal study (barium meal) is brought out by this case. Fortunately, the stone was first discovered by the roentgenologist in one of the films taken to show the outline of the stomach. The stone could very easily have been missed if barium was present in the large bowel and intestine overlying the kidney area. The gastro-intestinal symptoms completely disappeared following the removal of the calculus pyonephrotic kidney.

(2) **Biliary Type:** This type of symptom is not commonly observed in diseases of the upper urinary tract and is more likely to result from mechanical and pressure effects than from reno-hepatic reflexes. The diseases of the upper urinary tract most frequently confused with diseases of the biliary tract are movable kidney, congenital or acquired hydronephrosis, tumors or cysts of the kidney and occasionally renal or ureteral calculi. The presence of one or more ob-

Fig. 3. Case 1: The plain roentgenogram (on the right) shows a large triangular calculus in the left renal region just above the tip of the ureteral catheter. The bilateral pyelograms (on the left) show a relatively normal right kidney pelvis with abnormal course of the ureter at the ureteropelvic junction and a large left calculus pyonephrotic kidney. These films were taken about 18 hours following the ingestion of barium for a gastro-intestinal study.

jective signs in the right upper quadrant, i.e., palpable mass, localized muscle spasm or rigidity or tenderness together with digestive symptoms may lead to an erroneous diagnosis of cholecystitis or cholelithiasis and an unnecessary operation in any of the above mentioned conditions. The author has observed 5 such cases, viz., calculous pyonephrosis (Case II), renal calculi with hydronephrosis (Case III), ptosis (Case VII), hypernephroma, and perirenal tumor. Not infrequently patients with renal diseases exhibit an idiosyncrasy or intolerance to certain foods, especially fatty foods, which is incorrectly attributed to a disease of the liver or gall bladder.

Cases of jaundice diagnosed as cholelithiasis and proved to be due to movable kidneys have been reported by MacLagan and Treves, White, Fenwick, Lawrie, Sherren and others. At times it may be extremely difficult to differentiate between these two conditions as the major symptoms, jaundice and biliary colic, occur in both conditions. However, the fact that attacks of pain at night are rare with movable kidney and that the radiation of pain is characteristic in cholelithiasis aid in establishing the correct diagnosis. Rolleston explains the jaundice and biliary colic produced by a movable kidney in the following manner: The peritoneum over the kidney is continuous with that covering the duodenum and common bile duct and any undue motility of the kidney will lead to traction on and narrowing of the duodenum and bile ducts; at the same time there may occur a displacement of the gall bladder, kinking of the cystic duct and even a torsion of the bile ducts. According to Sherren, the association of jaundice with movable kidney appears to be first recorded by Brochin in 1854 and next by Litten in 1880. The same mechanism may be invoked in the production of jaundice and other biliary symptoms in those cases in which a large tumor of the kidney or a collection of blood, pus or urine in the perirenal space exerts pressure on the posterior peritoneum and adjacent structures. Mathe has recently reported a case of spontaneous rupture of the kidney pelvis resulting in perinephritic abscess and producing jaundice.

**Case II:** J. M., 41 years, Greek, male, employed as a tin mill worker in U. S. A. for past 8 years. He was seen in consultation for the first time on November 28, 1930. He complained of sharp pain in the right upper quadrant. Onset of illness dates back 13 years at which time he was living in Greece and he developed an attack of sharp pain in the right upper quadrant which radiated around to the back and up to the right shoulder and also across the abdomen. This attack was accompanied by chills, fever, nausea but no vomiting. The attack lasted about one hour. Following this episode, the patient stated that he was sick off and on for three months during which time he had similar attacks every two to three days. He thought he had jaundice, itchy skin and clay colored stools. He also noticed blood and mucus in his stools. In 1918, he was subjected to an appendectomy in Athens, Greece, with no relief of symptoms. Following this operation, the pain



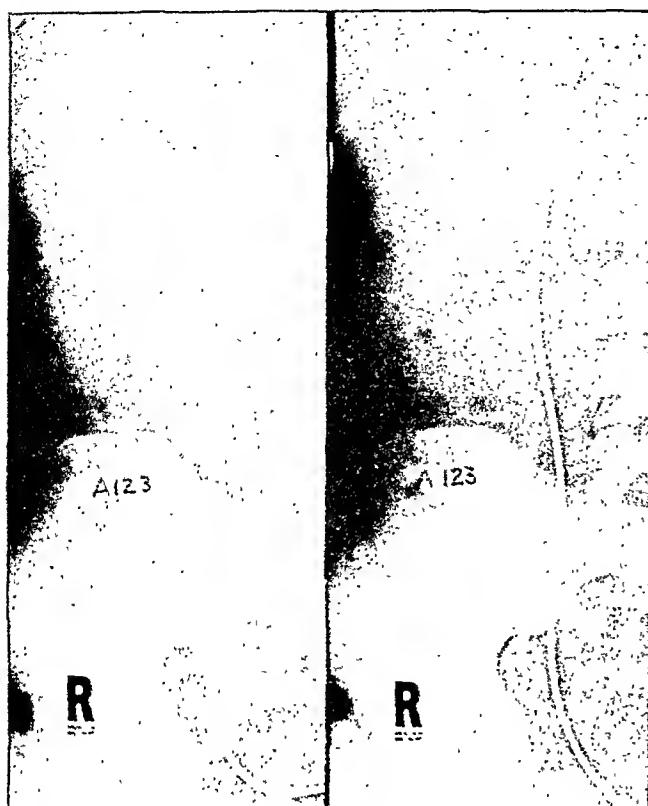


Fig. 4

recurred at intervals of three to five days with increasing severity and at times required hypodermic injections for relief. The pain was occasionally brought on by eating fatty foods. He complained of marked digestive disturbances, i.e., nausea, epigastric discomfort, belching, eructations, flatulency and constipation. In the past four months, the attacks of pain in the right upper quadrant and the digestive disturbances had become progressively worse and the patient lost about 20 pounds in weight. He consulted a surgeon who made a diagnosis of cholelithiasis and advised hospitalization.

The patient also gave a definite history of urinary disease but apparently little attention was paid to these complaints. He stated that he had frequently passed "gravel," about the size of a pea, and had pus in his urine for the past 13 years. He had hematuria at least once a year which preceded or followed the passing of a stone. He also complained of dysuria, burning and frequency during the day and night. He stated that the attacks of pain described above were relieved by the passing of a stone.

He was admitted to the hospital on November 16, 1930. *Physical examination* was essentially negative except for an ill-defined mass in the right upper quadrant which was accompanied by slight muscle spasm. There was tenderness over the mass but none was elicited in the right lumbar region or right lower quadrant. The leucocyte count was normal. The urine contained 30 to 40 p.c. and 20 to 30 r.b.e. per h.p.f. Roentgenograms of the gastro-intestinal tract following the ingestion of barium sulphate were made but were reported negative. Unfortunately, a plain plate of the genito-urinary tract was not taken and in the other plates barium covered the renal and ureteral regions.

On November 19, 1930, an *exploratory laparotomy* was performed. The gall bladder, stomach and intestines appeared to be normal. In the right renal region was a large mass about the size of a child's head which was an enlarged kidney. Nine days later, a urological consultation was requested. On November 29, 1930, *cystoscopy* and *pyelography* revealed a non-functioning calculous pyonephrosis on the right side. There were four shadows (cal-

Fig. 4. Case 2: The plain roentgenogram (on right) with ureteral catheter in place reveals the shadows of four calculi in the right kidney region. The pyelogram (on left) shows partial filling of a large right pyonephrotic kidney. The pyelographic medium obscures the shadows of the calculi.

culi) in the right kidney area (Fig. 4). On December 5, 1930, a nephrotomy was done and about one quart of thick green pus was removed. None of the stones were recovered. He was discharged from the hospital on December 24, 1930, to recuperate at home with the intention of returning in several months for a nephrectomy. While at home he developed "la grippe" followed by pneumonia and empyema of the right lower lung. He returned to the hospital and a thoracotomy was done on February 20, 1931. He recovered from this operation and was discharged on March 29, 1931, with a draining sinus leading to his kidney and a sinus leading to the pleural cavity. Both sinus tracts were treated by Dakinization but failed to close. On August 18, 1931, a nephrectomy was done and he made an uneventful recovery. Both sinus tracts persisted and subsequently operations were performed to close these sinuses.

*Comment:* In this case, the biliary symptoms were due to the pressure of a large calculous pyonephrotic kidney on the duodenum and biliary passages. In other words, the symptoms were mechanical in nature. It was unfortunate that insufficient attention was paid to the urinary symptoms and that an accurate past history was not obtained as the patient undoubtedly would have been saved an unnecessary exploratory laparotomy. This case also emphasizes the value of a plain roentgenogram of the intestinal tract as a preliminary routine measure in every gastro-intestinal or gall bladder roentgenographic study. Undoubtedly, if such a plate had been taken without the presence of barium in the bowel, the shadows of the calculi in the region of the right kidney easily would have been detected. It is interesting to note that this patient also showed an idiosyncrasy to fatty foods which was attributed to a biliary disease.

*Case III:* M. G., 65 years, female, widow, housewife. She was seen first in the gastro-enterological department of the Sinai Hospital out-patient clinic on February 8, 1934, complaining of pain in the right upper quadrant. She had been troubled with attacks of severe pain in this region for the past 10 years. At times the pain radiated around to the right lumbar region and up to the right shoulder and occasionally passed down to the right lower quadrant. This pain was not related to eating, exercise or posture. Occasionally the attacks of pain awoke the patient from her sleep. The pain was accompanied by nausea but no vomiting, chills or fever. The patient also complained of epigastric discomfort, eructations and heart burn. There was no history of jaundice or clay colored stools. At the onset the attacks of pain recurred at intervals of 3 to 4 months but in the past 6 months the pain had become more severe and occurred once or twice a week. There were no urinary symptoms other than nocturia. In the out-patient department a diagnosis of "gall bladder disease" was made and hospitalization advised.

The patient was admitted to Sinai Hospital on June 10, 1934. *Physical examination* was negative except for a palpable right kidney, tenderness in the right upper quadrant and a positive right ureteral point (Legge's sign). The urine was negative and the leucocyte count normal. A *plain roentgenogram* of the abdomen revealed an oval shadow about the size of a lima bean in the right upper quadrant. A gall bladder visualization was done and the report was that this shadow was in the gall bladder. In view of the normal findings in the urine and blood, the

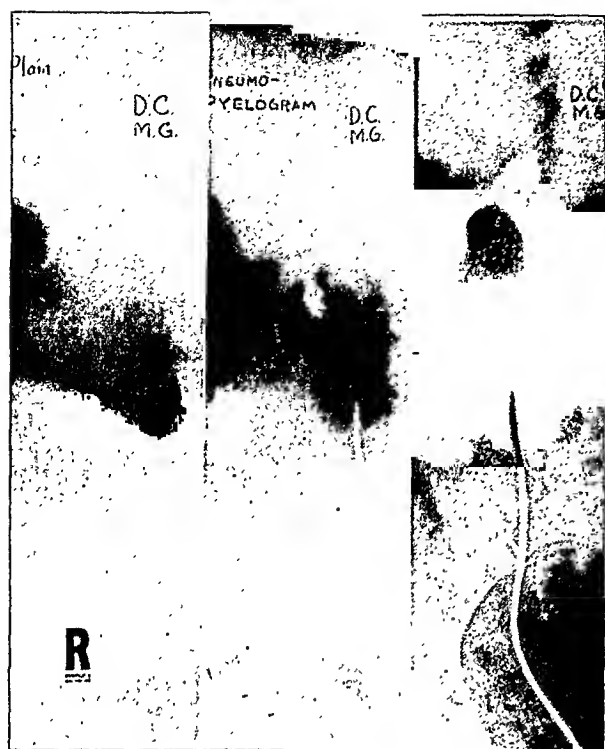


Fig. 5

presence of objective signs of renal pathology and the indefinite type of abdominal pain, cystoscopy and pyelography were performed. The aforementioned shadow was found to be within the right kidney as determined by pneumopyelography and stereoscopic ureteropyelograms (Fig. 5). On June 14, 1934, a pyelolithotomy was performed. Following the removal of the stone, the gastrointestinal symptoms and abdominal pain disappeared and have not returned to date.

*Comment:* This case illustrates the association of gastro-intestinal symptoms simulating cholelithiasis with renal lithiasis. The diagnostic problem presented in this case was solved by pyelographic study.

(3) *Appendiceal type:* It is a significant fact that pain in the right lower quadrant is seldom due to disease of the appendix in the absence of other signs and symptoms of this condition, i.e., fever, leucocytosis, tenderness, nausea and vomiting. Certain diseases of ureter (stone, stricture) and kidney (stone, hydronephrosis, pyelonephritis) may present a symptomatology similar to appendiceal disease which leads to frequent errors in diagnosis. As a rule, the occurrence of gastro-intestinal symptoms is not observed as frequently in diseases of upper urinary tract as in appendicitis. The lesions in the upper urinary tract most commonly confused with acute appendicitis are acute pyelitis or pyelonephritis, renal or ureteral stricture, ureteral calculus and hydronephrosis, respectively.

Hunner reviewed 100 cases of ureteral stricture and found that 30 of these patients had been subjected to an appendectomy. Loring has reported a case of right renal ptosis producing symptoms of an acute appendicitis. The Author has recently observed two cases of perinephritic abscess which were incorrectly diagnosed as acute appendicitis, one of these patients was subjected to an appendectomy. Too often, these patients are subjected to a needless abdominal operation and

Fig. 5. Case 3: On the right side the plain roentgenogram shows a large oval shadow situated between the 11th and 12th ribs which was mistaken for a large gall stone. In the center, the pneumopyelogram shows the shadow to be within the kidney outline. On the left, a stereoscopic pyelogram shows the shadow to be located at the junction of the pelvis and upper major calyx.

shortly there after pass a stone or have a recurrence of symptoms in an exaggerated form a few days or weeks later (Case IV). In view of these diagnostic difficulties and unpleasant postoperative experiences, it would seem advisable to take a plain roentgenogram of genito-urinary tract as a routine examination measure in every case of pain in the right lower quadrant but unfortunately this is not always obtained either because of the patient's poor financial condition or the surgeon's desire to operate. Certainly, this procedure is indicated in every doubtful case as the added expense may be adequately compensated by finding a stone in the ureter or pelvis whereby the cost of an abdominal operation is eliminated.

One cannot emphasize too strongly the importance of a thorough urological examination in those patients presenting indefinite appendiceal syndromes with concomitant renal symptoms to confirm the diagnosis of the former or determine the precise nature of the ureteral or renal lesion (Case V). Occasionally in spite of a urological study, a correct differential diagnosis cannot be made, especially in cases of retrocecal appendicitis with periappendicular changes which may give rise to a ureteritis or peri-ureteritis with interference to the urinary flow and resulting hydronephrosis. The Author is of the opinion that in doubtful cases and in those cases extremely difficult or impossible to diagnose accurately, it is best to err on the safety and subject the patient to an appendectomy rather than run the risk of developing a peritonitis (Case VI).

*Case IV:* F. W., 19 years, male, clerk was referred by Dr. M. Miller. The patient was first seen on July 29, 1930. The patient's history was extremely interesting. On November 15, 1929, patient developed sudden sharp pain in the right lower quadrant accompanied by nausea and vomiting but no chills or fever. Pain lasted 15 minutes and recurred one hour later. No urinary symptoms. Four days later had a similar attack but the pain radiated to the groin, and the following day had another attack. There was no history of hematuria or passing of stone or of urinary symptoms. On November 20, 1930, he was referred to a surgeon who advised taking a roentgenogram of the genito-urinary tract which was negative. The surgeon, who also practiced urology, failed to make a cystoscopic examination but removed the appendix. On the 10th postoperative day, the patient had another attack of right renal colic lasting 4 hours and requiring morphine for relief. He was discharged from the hospital on the 12th postoperative day and was in good health until July 26, 1930, when he developed right renal colic and again two days later. In the latter attacks the pain was accompanied by nausea, vomiting and epigastric distress. There were no urinary symptoms. The urine contained an occasional r.b.c.

*Cystoscopic and pyelographic examination* was performed on August 1, 1930, and revealed a double (fused supernumerary) kidney on the right side with a complete duplication of the ureter. There was a small calculus (2 mm. in diameter) about 3 cm. up in the ureter leading to the lower renal segment. The following day the patient passed this small stone.



Fig. 6 A

*Comment:* This case illustrates the occurrence of appendiceal symptoms secondary to an impacted calculus in the lower third of the ureter. It was rather surprising to learn that this patient had been seen by a surgeon who practiced urology and who failed to make a cystoscopic examination. Obviously, the latter was misled by the negative findings of a flat plate of the genito-urinary tract.

*Case V:* I. A., 33 years, male, was referred by Drs. Ullman and Zinberg. He was seen for the first time on July 23, 1934. For the past four to five months he has complained of a dull pain in lower abdomen in the midline which lasted a few minutes and recurred at irregular intervals. For the past month, the pain has shifted to the lower right quadrant and has become cramp-like in character. The pain was not related to meals or exercise and was not accompanied by chills or fever. There was nausea but no vomiting. Marked constipation was present. There were no urinary complaints. Three days prior to admission to the hospital, he had the last attack and consulted a surgeon who made a tentative diagnosis of chronic appendicitis and advised hospitalization.

He was admitted to the hospital on July 22, 1934. *Physical examination* was negative. The leucocyte count was normal. The urine contained several r.b.c. and p.c. which was the first inkling of the presence of a urinary disease. *Cystoscopy and pyelography* were performed on July 23, 1934, and revealed a large calculus in the middle calyx of a congenital crossed dystopic kidney (Fig. 6, A and B). The anomaly was a unilateral elongated kidney of the sigmoid type. Operative removal of the calculus was advised but has been postponed by the patient.

*Fig. 6 A. Case 5: Plain plate with catheters in both ureters showing a large shadow opposite the junction of the 1st and 2nd lumbar vertebrae. Note the abnormal course of the left ureteral catheter.*

*Comment:* Gastro-intestinal symptoms present in this case were of the colonic and appendiceal type. The causative lesion was a stone in the crossed dystopic kidney. This patient was saved from an exploratory laparotomy by the finding of pus cells in his urine by the Internes. This abnormality in the urinary constituents was the first indication of the presence of a urinary disease and led to a cystoscopic examination which disclosed the true nature of the urinary disease causing the gastro-intestinal symptoms.

*Case VI:* S. H., 41 years, male, attorney. He was seen at home on March 25, 1930, complaining of sudden sharp excruciating pain in the right lower quadrant radiating up to the right lumbar region. Pain lasted about three hours and was accompanied by nausea and vomiting but no chills or fever. A history of dietary indiscretion on the previous day was obtained. There were no urinary symptoms present. The urine contained an occasional r.b.c. and p.c. Examination disclosed tenderness with muscle spasm in right lower quadrant and tenderness on deep palpation in the right lumbar region. Leucocyte count was 12,000 with 82 per cent polymorphonuclears. A tentative diagnosis of right ureteral calculus was made and cystoscopy advised. The family physician disagreed with the diagnosis and insisted upon calling a surgeon who made a diagnosis of acute appendicitis and advised operation. The patient was sent into the hospital on March 25, 1930, at 6 A. M. After much persuasion on the part of the urologist, a cystoscopic examination was performed before subjecting the patient to an appendectomy. At 10 A. M. a cystoscopy was performed and a wax tipped catheter was passed up the right ureter encountering an obstruction 14 cm. up which produced a scratch on the wax. Stereoscopic roent-

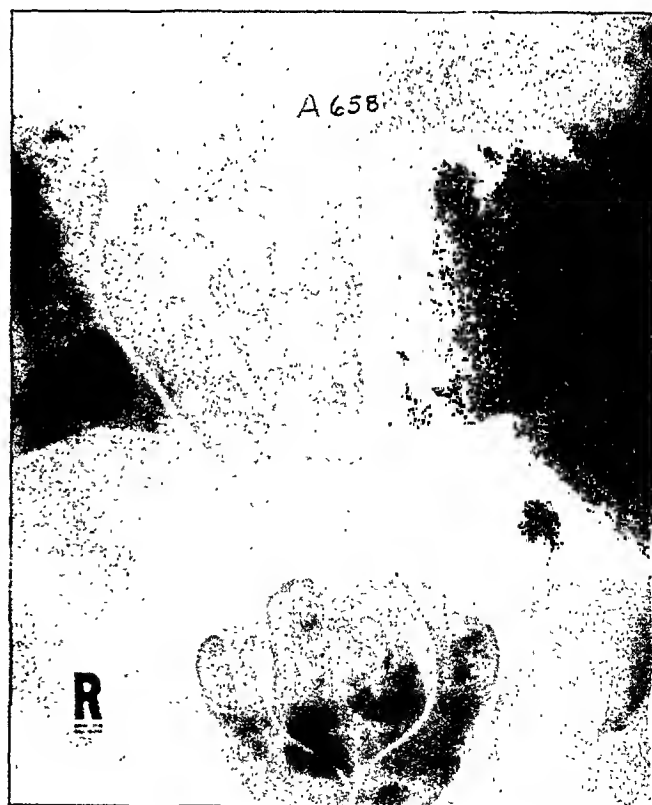


Fig. 6 B

*Fig. 6 B. Case 5: Bilateral stereoscopic pyelogram showing a unilateral elongated kidney of the sigmoid type. The shadow was determined to be a calculus in the upper calyx of the lower crossed dystopic kidney.*

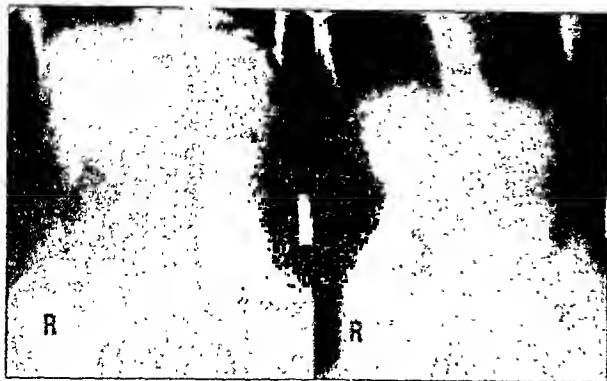


Fig. 7

genograms with the catheter in the right ureter showed a shadow along side of the catheter at the level of the 4th lumbar vertebra. On withdrawing the catheter a small black calcareous fragment together with some blood was seen to pass through the right ureteral orifice. A diagnosis of right ureteral calculus was made.

The pain in the right lower quadrant and right lumbar region persisted after cystoscopy. The family physician and surgeon failed to agree with the urologist that all the symptoms were due to the ureteral calculus and the associated hydronephrosis. They considered the possibility of an atypical or retrocecal appendicitis. At 10 P. M. of the same day, another surgeon was called in consultation who concurred in the diagnosis of an atypical acute appendicitis and advised appendectomy on the basis that it was best to err on the side of safety. At midnight, an appendectomy was performed under spinal anesthesia and a normal appendix situated anteriorly was removed. Following this operation, the pain in the right lumbar region and right upper quadrant persisted. Cystoscopy and pyelography were repeated on April 11th and a small calculus at the ureteropelvic junction was found. Following subsequent ureteral dilatations a small calculus was passed on June 5th, 1931.

**Comment:** This case illustrates the difficulty that may arise in differentiating between a ureteral calculus and a chronic or subacute appendicitis. Despite the positive findings, *i.e.*, scratch on the ureteral catheter and the presence of a shadow along side of the ureteral catheter on the plain plate, it was difficult to convince the family physician and surgeon that all the appendiceal symptoms were the result of a reflex disturbance. This case also illustrates the advisability of performing an appendectomy in the extremely doubtful or atypical cases or cases in which it is almost impossible to determine the exact causative lesion.

(4) **Colonic Type:** This type of syndrome may be associated with any disease of the upper urinary tract but chiefly with ureteral lesions because of the close proximity of the ureter to the colon on each side. Hunner has repeatedly stressed the association of gastro-intestinal symptoms with ureteral stricture in the female and has pointed out that the failure to recognize the presence of this lesion has been responsible for more needless and fruitless surgery than any other pathological lesion. Recently Morrison emphasized the importance and frequency of ureteral stricture as a cause of abdominal pain and has classified the gastro-intestinal manifestation according to the site of the stricture. He has pointed out that a stricture at the ureteropelvic junction producing a temporary or complete obstruction to the urinary flow usually causes

Fig. 7. Case 7: Pre-operative pyelo-ureterograms taken in the prone (H) and upright (E) positions indicating ptosis of the right kidney (grade II).

lateral epigastric pain with nausea and vomiting and during the quiescent period with good renal drainage is accompanied by an indefinite aching pain just below and lateral to the umbilicus. When the lesion occurs at the point where the ureter crosses the iliac vessels, the pain is referred to the inguinal region or somewhat medial to the usual site of appendiceal pain. The pain is usually insidious in onset, dull in character and lasts from one to three hours with frequent intermissions for days or weeks. If the lesion is present in the intramural portion of the ureter, the pain is referred to the suprapubic area and is accompanied by urinary symptoms. Ptosis of a kidney with kinking may produce essentially the same symptoms as a stricture in the upper third of the ureter (Case VII).

Patients with ureteral disease or movable kidney occasionally complain of tenderness along one side of the abdomen and on examination present areas of cutaneous hyperesthesia at various points about the umbilicus described by Morris, Hunner, Kummell and Legge. Many of these patients complain of abdominal discomfort after assuming an upright position (Case VII) and of irregular post-prandial discomfort which is often relieved by taking bicarbonate of soda, expelling flatus or evacuating the bowels. Constipation is a complaint which persists or is made worse by the use of cathartics or purgatives. In some cases diarrhea is the predominating symptom and may be so severe as to suggest an ulcerative colitis (Case VIII).

Occasionally, the chief complaint is frequent attacks of spasmodic or cramp-like pains which may be confined to one side of the abdomen or radiate downward and across to the opposite side (Case IX). Pyelographic study may reveal a dilated pelvis in a congenital or acquired hydronephrotic kidney (Smith, Author's case IX) or in a ptosed kidney (Case VII and VIII). The usual conservative measures fail to relieve the condition. At operation there are found numerous adhesions between the dilated pelvis and the posterior peritoneum and adjacent large bowel. The dilatation of the renal pelvis may be due to a congenital or acquired stricture in any part of the ureter or to adhesions, bands, aberrant vessels crossing the ureter or at the ureteropelvic junction.

Congenital anomalies of the kidney, *i.e.*, horseshoe kidney, sigmoid kidney, congenital ectopic kidney, frequently are confused with tumors of the intestines, pancreas, omentum, etc. Although these anomalies are often unaccompanied by subjective symptoms, pain or a sensation of pressure in the abdomen is relatively common. When these anomalous kidneys become infected or enlarged, gastro-intestinal symptoms are prominent but cause increased difficulties in diagnosis due to their atypical character and position. Pyelographic studies are essential to establish the correct diagnosis.

**Case VII:** O. E., 25 years, female, single, nurse, referred by Dr. Zinberg. She was admitted to Sinai Hospital on September 18, 1928, complaining of pain in the right upper quadrant. For the past 9 years she has been complaining of a dull pain in the right upper quadrant which occasionally radiated to the lower right quadrant and right inguinal region. At times the pain has been

rather sharp but never colicky. The pain had no relation to eating and appeared to be relieved by lying down and was worse after being up on her feet. The pain was accompanied by frequent spells of nausea and vomiting but no chills or fever. There were no urinary symptoms other than an occasional burning on urination. Her appetite was poor and she had lost 10 pounds in the past 3 months. She had been taking one to three morphine tablets (one-half grain each) daily for the relief of the pain.

The patient had been subjected to four abdominal operations and one minor operation in the search for the cause of her abdominal pain, viz. appendectomy (diagnosis: chronic appendicitis) 9 years ago; dilatation and curettage of uterus and suspension of uterus, 8 years ago; cholecystectomy (diagnosis: chronic cholecystitis) 3 years ago; tonsillectomy, 2 years ago; and a hysterectomy 1 year ago. The pain recurred after each operation. About 8 months ago, she was examined by another urologist who diagnosed her condition as bilateral ureteral strictures and gave the patient 8 ureteral dilatations at intervals of two to four weeks. No pyelographic studies were made.

Physical examination disclosed tenderness in the right lumbar region and right upper quadrant. There was a positive right ureteral point (Legge's sign). The lower pole of the right kidney was palpable when the patient was in the erect position. The urine was negative.

Cystoscopic and pyelographic study revealed a marked ptosis of the right kidney with a sharp kink in the right ureter about 2 cm. from the ureteropelvic junction (Fig. 7). On September 21, 1928, a nephropexy was performed and the patient made an uneventful recovery. The patient was followed for two years after operation during which time all symptoms disappeared and she gained 20 pounds.

*Comment:* The gastro-intestinal symptoms were due to a ptosis of the right kidney. Unfortunately, the patient had been subjected to four major abdominal operations and one minor operation in a fruitless search for the cause of her abdominal pain before an urological examination was requested. This case also emphasizes the importance and value of pyelography in horizontal and erect positions in the diagnosis of movable kidney. Undoubtedly if this procedure had been employed by the urologist, who saw the patient first, the correct diagnosis would have been made easily and the patient spared the suffering of eight ureteral dilatations.

*Case VIII:* L. G., 38 years, female, married, housewife, referred by Dr. H. Beek. She was admitted to Sinai Hospital on April 17, 1932, complaining of nausea, vomiting and diarrhea. The patient stated that 8 years ago she was confined for 4 weeks at another hospital receiving a modi-

fied Sippy treatment for a gastric ulcer. During her stay in the hospital she had her appendix removed. Her chief symptoms were dull pain in the epigastrium and right lower quadrant, belching, heartburn, alternate constipation and diarrhea. These symptoms recurred about 2 months after operation and she received further treatment for a gastric ulcer with no apparent relief. About 5 years ago the patient developed a marked diarrhea with vague abdominal pain and cramps which persisted for several months; such were attributed to an ulcerative colitis. A roentgenographic study of the gastro-intestinal tract at this time failed to disclose any pathological condition responsible for her symptoms.

Three years ago, she was referred for urological examination and a diagnosis of ptosis of the right kidney was made. Lumbar fixation of the kidney was advised but the patient refused. She was lost sight of until she presented herself for admission to the hospital on the above date. For 6 months prior to admission she had a marked exacerbation of all the gastro-intestinal symptoms. She complained of a persistent nausea and frequent vomiting after meals. She was having 6 to 8 soft watery stools daily. She had lost 35 pounds in the past 3 years.

Physical examination was negative except for slight tenderness in the right upper quadrant and in the right lateral epigastrium. Urine examination was negative. Cystoscopic and pyelographic studies were repeated and disclosed a marked ptosis of the right kidney with a kinking of the ureter (Fig. 8). A nephropexy and denervation of the right renal artery, vein and pelvis were performed. The patient made an uneventful recovery. She had been followed for the past 2 years during which time the symptoms have disappeared entirely and she has regained 25 pounds.

*Comment:* This case illustrates the various gastro-intestinal manifestations associated with a movable kidney. This case also illustrates the fact that the response to the same stimuli may be different in the same individual. The varied response to the reno-digestive reflexes in this patient resulted in a mistaken diagnosis of gastric ulcer, chronic appendicitis and ulcerative colitis respectively. This patient is an example of an individual predisposition to reno-digestive reflexes. This inherent tendency was also manifested by extreme nervousness, marked emotional instability and vasomotor disturbances.

*Case IX:* J. P., 52 years, male, grocer, was referred by Dr. F. T. Leitz. Patient was referred for urological study on June 1, 1932. Patient had been treated for "stomach trouble" for the past 10 years. He has had cramp-like pains in the lower left quadrant, which lasted 5 to 6 hours and recurred at intervals of 3 to 4 months. Patient described the pain as a constant

dull cramp-like pain in the lower left quadrant which radiated across the abdomen and occasionally passed around to the left lumbar region. Pain was accompanied by nausea and vomiting, particularly after eating. There was a moderate amount of epigastric discomfort, belching and eructation and heartburn. Patient also complained of a marked constipation, often passing 2 to 3 days without having a bowel movement. Between the attacks of pain, patient felt perfectly well but after the attack was left with a residual soreness in the left epigastric region which persisted for two days.

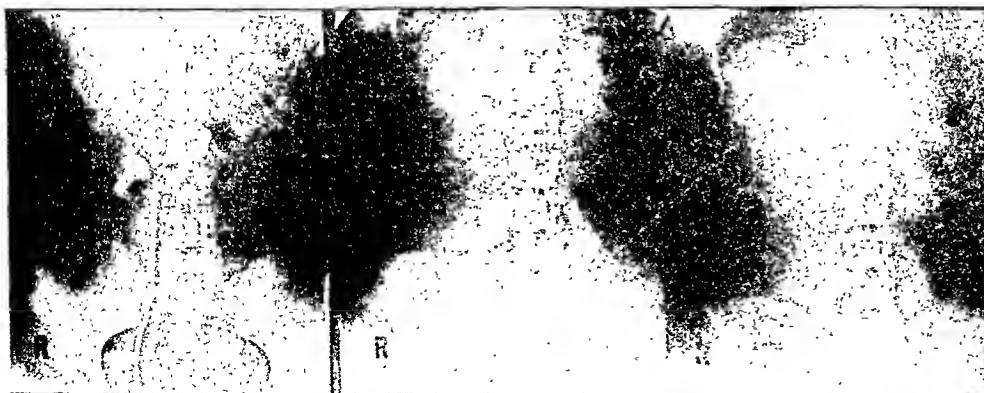


Fig. 8. Case 8: Pre-operative pyelograms of the right kidney. The roentgenogram on the extreme left was taken in prone position and the one in the center was taken in the upright position. On the extreme right is an eight minute retention plate showing a moderate amount of the dye retained within the renal pelvis.



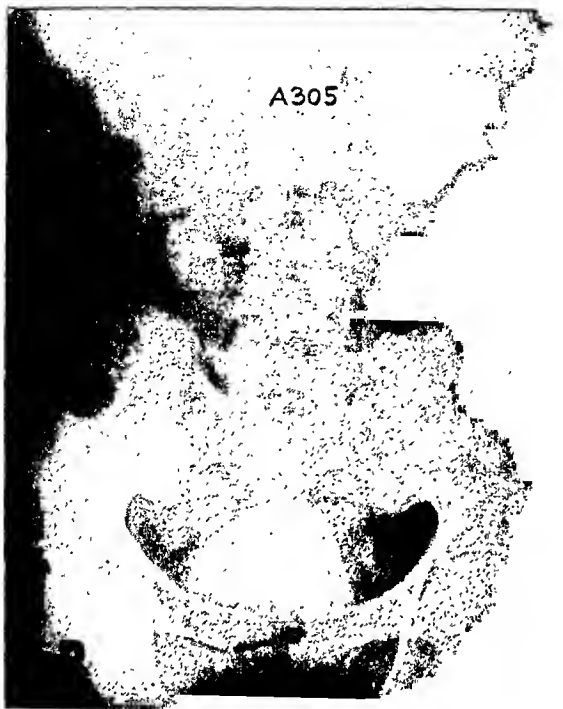


Fig. 9

The present attack began on May 25, 1932, and persisted for 4 days. Enemas were effectual but did not give complete relief. Sedatives likewise failed to give relief. Patient gave a history of diurnal frequency, q. 1 hr. and nocturia 2 to 3 times, hesitancy and burning. No hematuria or passing of gravel. Patient had been subjected to repeated gastro-intestinal X-ray studies, stomach analyses, proctoscopic examinations, etc. He was admitted to the hospital on May 29th.

*Physical examination* was essentially negative. Urine was negative except for an occasional pus cell. The leucocyte count was normal. Cystoscopy and pyelography were performed on June 8, 1932, and revealed a large hydronephrosis of the left kidney with an obstruction at the ureteropelvic junction (Fig. 9). On June 14, 1932, the left kidney was exposed under spinal anesthesia. There were marked dilatation of the pelvis which was of the extra-renal type and a constriction of the ureter at the ureteropelvic junction. The posterior peritoneum and descending colon were intimately adherent to the anterior surface of the pelvis for a distance of approximately 8 cm. These structures were dissected off the pelvis and a plastic operation was performed removing an elliptical piece of tissue from the anterior and posterior aspect of the pelvis. The stricture at the ureteropelvic junction was corrected by a Heinicke-Mikulicz repair. Patient made an uneventful recovery and was discharged from the hospital in two weeks.

Three months later he developed a sudden sharp pain in the operative area following the lifting of a heavy object and two days later presented a soft fluctuating mass in the upper end of the wound. Cystoscopic and pyelographic studies at this time revealed a rupture of the pelvis and a perinephritic abscess. Nephrectomy was done and the patient made an uneventful recovery. Following the operation, the patient has been observed for two years and there has been no recurrence of the gastro-intestinal symptoms.

*Comment:* The gastro-intestinal symptoms in this case were due to the adhesions between the descending colon and the pelvis of the kidney. Undoubtedly, the

Fig. 9. Case 9: Pyelogram showing a large left hydronephrosis. The dilation of the pelvis is of the extra-renal type. There is an abnormal obstruction of the ureter at the ureteropelvic junction which was found at operation to be due to a dense stricture at this point.

sequence of events was as follows: The stricture at the ureteropelvic junction produced a large hydronephrosis which became infected and as a result of the peripelvic infection, adhesions were formed between the pelvis and the descending colon and the overlying posterior parietal peritoneum. This lesion produced a mechanical interference with the function of the bowel which was responsible for the patient's intestinal symptoms.

(5) *Peritoneal Type:* This type is characterized by an abdominal syndrome simulating an intestinal obstruction or general peritonitis and is not as frequently observed as the other types. There are numerous references in the urological literature to the development of intestinal obstruction, or rather an apparent ileus, in the various diseases of the upper urinary tract. The earliest report of this phenomenon is by Desnos in 1887 who described two cases of ileus secondary to renal lithiasis. The majority of cases of ileus secondary to disease of the upper urinary tract has been associated with renal lithiasis (Desnos, Sternberg, Stewart, Quenu, Smith, Loeper, Gayet and Ricard, Seze and others) and with ureteral lithiasis (Legueu, Tixier, Gauthier and Clavel, Denechau and Prieur, Frugoni, Jankelson, Rinaldi, Ramon and others). Clavel reviewed the literature and found cases of ileus associated with many diseases of the upper urinary tract other than renal or ureteral calculi, viz. congenital or acquired hydronephrosis, ruptured hydronephrosis, renal tumors, polycystic disease, renal tuberculosis, pyelonephritis, nephrosis (Case XI), perinephritic abscess, perirenal hematoma, etc., but failed to mention its occurrence in cases of movable kidney. This phenomenon has also been observed in movable kidney by Plenz, DiMaio, Ducuing and Biscard and others. Ileus has also reported following various operations on the kidney, viz. nephrolithotomy (Albarran), pyelotomy (Iselin), nephropexy (Tansini, Chardonnek, Hildalgo and Cano), and nephrectomy (Caravan, Duvergey, Ouard, Ammon). Nogues maintained that development of a paralytic ileus following operations on the upper urinary tract may be due to one or more of the following causes, viz. (1) mechanical obstruction of the intestines produced by placing clamp on intestines; (2) mesenterico-aortic adhesions; (3) obstruction due to torsion or adhesions; (4) toxic manifestations of uremia; (5) traction of pedicle of kidney; and (6) action of anesthetic particularly spinal anesthesia, upon intestines. It is interesting to note that ileus has also been reported following operations on the bladder, prostate and seminal vesicles. The Author has recently observed a case of ileus following a bilateral vasectomy done under novocain infiltration anesthesia as a preliminary measure to prostatectomy.

The ileus associated with diseases of the upper urinary tract is of the adynamic or paralytic type and is accompanied by complete abdominal calm, although peristaltic movements suggesting a true intestinal obstruction are noted occasionally. At times it is extremely difficult to differentiate this apparent ileus from a genuine partial or complete intestinal obstruction.





Fig. 10

tion. One point that greatly aids in differentiating the apparent ileus associated with diseases of the kidney and ureter from true intestinal obstruction is the fact that in the former condition the pain precedes the abdominal distention while in the latter condition it follows the distention. Another useful observation is that the general status of the patient is less affected by a reflex ileus than by a true obstruction. Vomiting, *i.e.*, regurgitation of contents of stomach and small intestines or bile stained fluids, may occur in both conditions but fecal vomiting is rarely observed in ileus secondary to diseases of the upper urinary tract as only three such cases have been reported, *viz.* Desnos' two cases secondary to renal calculi, Ducuing and Giscard's case secondary to ptosis. The diagnosis of reflex ileus secondary to upper urinary pathology is confirmed by the presence of pain, tenderness or a mass in the renal region, the demonstration of renal pathology by ureteral catheterization or pyelo-ureterography and by the failure to discern a true intestinal obstruction roentgenographically (Case X).

Krechi has emphasized the importance of gas retention as a symptom of renal or ureteral disease. The same phenomenon is seen less frequently following ureteral catheterization, pyelography, hydronephrosis, pyonephrosis (Case XI), perinephritic abscess, etc. These patients complain of abdominal discomfort, particularly in the right upper quadrant, which is described as—"gas tries to come up but sticks somewhere." The inability to rid the stomach and colon of gas is due to a reflex disturbance originating in the kidney or ureter. Those cases may be mistaken for ileus or appendicitis and not infrequently are subjected to an exploratory laparotomy by inexperienced surgeons. The same phenomenon is occasionally seen in very nervous and highly emotional people.

Fig. 10. Case 10: Plain plate of the abdomen showing the marked distension of the large intestines by gas. The arrow points to a small calculus in the lower third of the left ureter which was responsible for the reflex ileus.

One cannot stress too strongly the necessity of establishing a correct diagnosis and determining the etiological factor in every unexplained case of intestinal obstruction or peritonitis in order to avoid an unnecessary operation. The following procedures often prove to be invaluable diagnostic aids, *viz.*, urine examination for blood and pus cells; plain roentgenogram to determine the presence of a renal or ureteral calculus and retrograde or intravenous pyelography with the patient in the flat and upright positions to rule out a movable kidney.

*Case X:* L. R., 45 years, white, male, sculptor was referred by Dr. M. Baylin. Patient was seen first on July 3, 1933, at 7 P. M. complaining of sharp pain in the lower left quadrant. The pain radiated up to the left lumbar region and across the abdomen. Pain awoke patient at 4 A. M. and recurred several times during the day. Patient also complained of epigastric discomfort, belching and abdominal distension which he described as "being ballooned up." He was given several enemas without relief. There were no urinary symptoms, chills or fever. The urine contained an occasional pus and blood cell. A tentative diagnosis of left ureteral calculus was made and hospitalization for complete urological study advised but was refused by the patient.

At 11 A. M. on the following day (July 4th), the family of the patient insisted upon calling a general surgeon who thought the patient had an intestinal obstruction and sent the patient to the hospital. At 2 A. M. on July 5th, I was requested to see the patient again in consultation with the surgeon and an internist. The patient still complained of sharp pain in the left lower quadrant. There was marked abdominal distension present with slight tenderness in the left lower quadrant and left lumbar region. Temperature and pulse were normal. The urine showed an occasional red blood cell. My impression was that the patient was still suffering from an impacted calculus in the lower third of the left ureter and that the abdominal distention was due to reflex irritation. The patient was given turpentine stipes for one hour followed by one ampule (1 c.c.) of surgical pituitrin and obtained almost immediate relief after evacuating a large amount of feces and expelling a great deal of flatus.

At 10 A. M. (July 5th) a *cystoscopic examination* was performed. A wax tipped catheter was passed up the left ureter and encountered an obstruction 2 cm. up which produced a scratch on the wax. A roentgenogram of the genito-urinary tract showed a small shadow in the lower left ureter and a marked distention of the bowel with gas (Fig. 10). Stereoscopic roentgenograms were taken with a catheter in the ureter and showed a small stone. There was a moderate hydronephrosis present. A no. 6 F. ureteral catheter was passed beyond the calculus and left in place for 48 hours. It was removed after injecting 8 c.c. of sterile olive oil through the catheter. On July 9th, the patient passed a small stone and was discharged from the hospital the following day.

*Comment:* This case illustrates the diagnostic difficulties occasionally encountered in differentiating between a true intestinal obstruction and an apparent adynamic ileus due to the reflex disturbances from an impacted calculus in the lower third of the ureter. The use of surgical pituitrin and high medicated enemas afforded the patient immediate relief from the abdominal distention. Following ureteral dilatation and the

insertion of a retention catheter in the left ureter, the stone was passed.

*Case XI:* J. F., 35 years, male, clerk was referred by Dr. A. Hornstein. He was seen for the first time on January 24, 1930. The onset of present trouble dates back 12 years when he developed sudden sharp pain in the right lumbar region radiating around to the right upper quadrant but not to the groin. The attacks of pain lasted several hours and recurred at intervals of one to two months up to four months ago. The pain was not accompanied by nausea, vomiting, chills or fever. There were no associated urinary symptoms. About 4 months ago, he developed sharp pain in the right lumbar region which at first radiated to the groin and became localized in the right renal region as a dull dragging pain. This attack lasted about 6 hours and was accompanied by no unusual symptoms other than a moderate diurnal and nocturnal frequency and burning on urination.

On January 14, 1930, patient developed generalized pain over his entire body and called his physician who thought he had "la grippe." Two days later he developed a dull pain in the right lumbar region which did not radiate. The pain was accompanied by nausea, vomiting, chills and fever. The patient was kept in bed for two weeks. The vomiting persisted but on the 21st of January became rather severe. There was marked abdominal distention, high fever and chills. The family physician thought that the patient had an acute intestinal obstruction and advised hospitalization. In view of the history of renal colic in the past and the presence of frequency, burning and pus in the urine during the present illness, a urological consultation was sought.

On abdominal examination, there was marked distention of the right abdomen. There was tenderness on palpation in the right upper quadrant and right lumbar region. There was a moderate amount of spasticity of the muscles of the right upper quadrant. There was a tympanic note over almost the entire abdomen. All ill-defined mass could be palpated in the right upper quadrant. A voided specimen of urine showed a slight trace of albumin and many pus and red blood cells. A white blood count was 18,000 with 82% polymorphonuclears leucocytes.

On January 24, 1930, *cystoscopy and pyelography* were performed and a diagnosis of a large pyonephrotic kidney was made. There was a very sharp angulation in the ureteropelvic junction. There were no shadows indicating stones in the kidney region. Patient became progressively weaker and more toxic. There was a sudden rise in the blood urea to 160 mgm. per cent. On February 3, 1930, a nephrectomy was done under gas anesthesia and about 500 c.c. of thick, greenish pus was removed. Patient made an uneventful recovery and on April 4, 1930, a nephrectomy was done. Convalescence was uneventful.

*Comment:* This case illustrates the association of symptoms of an adynamic ileus secondary to a large pyonephrotic kidney. Drainage of the infected kidney resulted in a prompt relief of symptoms. The infected kidney was removed and there has been no further return of symptoms.

### SUMMARY

The purpose of this paper is to point out the various types of gastro-intestinal symptom that may be associated with diseases of the upper urinary tract and to emphasize the diagnostic difficulties encountered in differentiating between the latter conditions and disease of the gastro-intestinal tract. However, the difficulty of making a diagnosis of disease of the upper urinary tract is greatly enhanced by the fact that there are several clinico-pathological entities which singly or in combination, produce corresponding gastro-intes-

tinal and urinary disturbances, the preponderance of the symptoms depending on which pathologic changes dominate the field. Recognition of the following entities is of importance from the standpoint of establishing an accurate diagnosis: (1) the production of real pathological changes in the gastro-intestinal tract by diseases of the upper urinary tract; (2) the development of symptoms suggestive of disease of the upper urinary tract by extra-renal disease, particularly of the intra-abdominal organs; and (3) the concomitant occurrence of lesions of the upper urinary and gastro-intestinal tracts.

1. *Gastro-intestinal lesions caused by disease of the upper urinary tract:* Not infrequently the information gathered by the various diagnostic methods does not enable the urologist or clinician to establish an accurate diagnosis of the underlying renal or ureteral lesion or to determine the extent of pathologic changes produced in the upper urinary and the gastro-intestinal tracts due to the fact that the usual subjective symptoms and objective findings may be negative, absent, misleading or overlooked.

It is not generally recognized that various pathological changes may occur in the mucous membrane of the stomach and intestines in many diseases of the upper urinary tract, particularly in the acute or chronic nephritides. In the acute or subacute forms of nephritis with edema or those of the hemorrhagic type including the acute nephroses, well defined changes are observed in the gastro-intestinal tract, i.e., thick mucus covering the lining of the stomach, swelling, distortion and disintegration of the glands of the stomach and intestines. In the chronic forms of nephritis with edema, the pathological changes in the gastro-intestinal tract are more extensive, especially in the pyloric area. The mucosa appears to be of a grayish color and in some areas is congested and of a reddened color with ecchymotic patches or small hemorrhagic ulcerations. The glands of the stomach and intestines lose their characteristic appearance as a result of enlargement and distortion. The glandular cells show marked degenerative changes, i.e., cloudy, granular, fatty or mucoid degeneration. There are also changes in the submucosa and muscularis varying from round cell infiltration to fibrotic changes. In the chronic forms of nephritis without edema but with hypertension, the inflammatory and degenerative processes are replaced by extensive fibrotic changes in all layers of stomach and intestines resulting in an atrophic gastritis or enteritis. Punctuate hemorrhage with areas are seen in the mucosa of the stomach and small intestines. Superficial ulcers are also observed in the stomach and intestines which gradually increase in size and produce extensive changes in underlying layers. Sloughing ulcers are not infrequently found in the large intestines associated with profuse diarrhea and simulate the clinical picture of an ulcerative colitis. Occasionally these ulcerative lesions cause extensive secondary fibrotic changes in all the layers of intestines which lead to an occlusion of the intestinal lumen with the clinical signs and symptoms of true intestinal obstruction as occurred in the case reported by Reynier and Le Chevallier. Any lesion of the urinary tract wherein an obstruction or chronic infection supervenes resulting in a chronic pyelonephritis, may

produce changes in the gastro-intestinal tract similar to those already described.

Gastro-intestinal disturbances also may develop during the course of certain diseases of the kidney, i.e., chronic diffuse nephritis, arteriosclerotic kidneys, polycystic disease, etc., as result of the cardio-vascular disturbances attending this condition. With the onset of decompensation in the circulatory system, chronic passive congestion of the gastro-intestinal tract ensues. An early enlargement of the liver and congestion of the gastro-intestinal tract develop as a result of portal stasis. Changes in gastric and intestinal secretory and motor functions occur resulting in the production of digestive symptoms of varying intensity.

Another type of gastro-intestinal lesion caused by disease of the upper urinary tract is the development of a peritonitis following the spontaneous or traumatic intraperitoneal rupture of an infected or hydronephrotic kidney as observed by Gottstein, Kappel, Rost and others. A different type is the development of a fistula between the kidney and the gastro-intestinal with subsequent irritation and ulceration of the intestinal walls which occurs as a result of a spontaneous or traumatic rupture of a normal or pathological kidney (Higgins and Hicken, Vermooten and McKeown and others) or following operative injury to the intestines during a renal or ureteral operation (Young, Davis).

2. *Symptoms of renal disease produced by extra-renal conditions:* There is scant reference in the urological literature to extrarenal conditions which may be accompanied by symptoms suggestive of pathology in the upper urinary tract. In this connection, it is important to mention briefly the fact that the lower genito-urinary tract, i.e., pathologic conditions of the prostate, seminal vesicles, and vas in the male (Goldstein, Block) of the pelvic organs in the female (Dannreuther, von Lichtenberg), and the urethra in both sexes (Folsom, Stevens), may produce symptoms suggestive of upper urinary tract pathology or serve as the principal etiologic factor in the development of pathologic conditions of the entire urinary tract.

It is also well to point out that a diagnosis of appendicitis is not infrequently made in patients suffering from an acute infection of seminal vesicles or prostate, especially on the right side. Careful rectal examination will reveal the lesion responsible for the appendiceal symptoms. Chronic infections of these same organs may produce an afebrile right iliac pain which is frequently mistaken for chronic appendicitis but examination of the strippings from the prostate and seminal vesicles reveals an excessive amount of pus. The pain in the inguinal region produced by an acute vasitis has also been mistaken for an acute appendicitis.

Every urologist has undoubtedly had the unfortunate and unpleasant experience of making an incorrect or mistaken diagnosis of disease in the upper urinary tract in the presence of abnormalities or lesions of the gastro-intestinal tract, especially of the appendix, pylorus, intestines, biliary tract, spleen, etc. Stevens has reported two cases which illustrate this point. In his first case, a diagnosis of two ureteral calculi was made by cystoscopy and radiography and at operation a large tortuous appendix containing two fecoliths was found adherent to the ureter. In the second case, the chief symptoms were pain and tenderness in the right upper quadrant which were attributed to a ptosis of

right kidney with kinking of the ureter. Nephropexy was performed with no relief and one month later an exploratory operation revealed a carcinoma in the first portion of the transverse colon. Surgeons and urologists not infrequently encounter cases in which the inflamed appendix is situated retroceally or is intimately adherent to the parietal peritoneum overlying the kidney or ureter and is accompanied by urinary symptoms, pus or blood cells in the urine and pain referred anteriorly to kidney or ureteral regions or posteriorly to the costovertebral angle. These are the cases which are commonly confused with an acute infection of the kidney (pyelonephritis) or perinephritic abscess and are extremely difficult to diagnose even with the assistance of a thorough urological examination. It is in this type of case in which no gross urological lesion can be demonstrated that the author believes it is best to perform an exploratory operation rather than run the risk of the development of a localized abscess or general peritonitis.

It is also well to bear in mind that pathologic conditions in organs other than the above, i.e., lungs, adrenals, heart, lymphatics, spinal cord, etc., occasionally may produce symptoms suggestive of disease in the upper urinary tract.

3. *Concomitant occurrence of lesions in the upper urinary and gastro-intestinal tracts:* Although this phenomenon is relatively uncommon various concomitant lesions or anomalies of the upper urinary and gastro-intestinal tracts have been reported. The combination observed most frequently is a lesion of the kidney or ureter associated with a lesion of the biliary tract (Case XII). Chauffard and Colali have reported cases of renal and biliary lithiasis and the Author has also observed two similar cases. Stevens has reported several interesting cases of co-existing lesions of the upper urinary and gastro-intestinal tracts, viz., (a) hepatitis associated with ureteral strictures, and pyelonephritis, (b) hepatitis associated with pyonephrosis, (c) cirrhosis of liver and diabetes associated with rotation of right kidney and stone in left ureter, (d) large Riedel's lobe of liver associated with tumor of right renal pelvis, and (e) carcinoma of sigmoid associated with left ureteral stricture.

*Case XII:* I. D., 52 years, male, married, hat cleaner. He was first seen in the medical clinic of the out-patient department of the Sinai Hospital on June 9, 1932, complaining of epigastric discomfort and pain in the right upper quadrant. He stated that for the past 25 years he has suffered from epigastric discomfort, belching, heartburn, dull pain in right upper quadrant and nausea which was especially marked after eating fried or fatty foods and was relieved by taking bicarbonate of soda. There was no history of jaundice or clay colored stools. The pain was dull in character and occasionally radiated around to the lumbar region and to the right inguinal region. In February, 1932, he had a bilateral hernioplasty done at another hospital. Following this operation, he complained of dull pain in both groins radiating up to the lumbar regions which was more pronounced on the right side. He had lost 25 pounds in the past 4 months. He also gave a history of frequency. (q. 1 hour, during the day and 4 to 6 times at night), hesitancy, urgency, and incomplete bladder emptying. He had never had renal colic (?) or hematuria. Physical examination essentially was negative. The urine and blood examinations were also negative.

In the medical clinic a diagnosis of "chronic cholecystitis" with cholelithiasis was made but no roentgenographic studies were made. He was referred to the genito-urinary clinic for further study. Cystoscopy and

pyelography were performed on June 10, 1932. The plain roentgenogram of the abdomen revealed a group (10 to 12) of small shadows in the gall bladder region and an oval shadow, about the size of a lima bean, opposite the third lumbar vertebra in the line of the ureter. Pyelographic studies showed that the latter shadow was a calculus in the upper third of the ureter and the right kidney was a large pyonephrotic sac (Fig. 11). The patient was admitted to the Sinai Hospital on August 19, 1932, and 9 days later the pyonephrotic kidney and the upper third of the ureter containing the stone were removed. Recovery was uneventful. The patient has been followed for two years and his general health has been excellent. The majority of his gastro-intestinal symptoms have disappeared, although he still complains of epigastric discomfort occasionally following dietary indiscretion. He has been advised to have his gall bladder removed but refused.

*Comment:* This case is presented to emphasize the occurrence of concomitant lesions of the upper urinary and biliary tracts, viz. right ureteral calculus, right pyonephrosis and cholelithiasis.

It is often difficult to determine whether both lesions have a common etiological factor or are independent of each other. Helwig and Schutz have described a renohepatic syndrome in which certain pathological changes in the kidneys, *i.e.*, parenchymatous degeneration simulating a nephrosis, are caused by certain pathological changes in the liver which are usually secondary to long standing gall bladder diseases. Ferranini has observed similar changes following hepatic cirrhosis. Renal disease is known to occur as a result of pyloric or high intestinal obstruction. In this condition, gastric tetany may appear and signs and symptoms of a severe toxemia may be manifested. Brown, Eusterman, Hartman, and Rowntree reported 11 cases of duodenal toxemia resulting from high intestinal ob-

struction and found changes in the kidneys which they described as either a diffuse nephritis or nephrosis. Zeman, Friedman and Mann described a toxic degenerative nephrosis in four clinical cases of pyloric obstruction and obtained similar findings experimentally following occlusion of the pylorus in cats. Cooke observed calcification and degeneration of the renal tubules in 6 fatal cases of pyloric stenosis with excessive vomiting. The pathological changes in the kidney were attributed to an excessive alkalosis. Occasionally, an acute exacerbation of a pre-existing chronic nephritis, manifested by toxic symptoms of uremia or alkalosis, may occur during the course of treatment of a gastric disease. Hardt and Rivers observed toxic symptoms in two patients receiving alkaline medication for peptic ulcer. Tucker reported the development of fatal uremia following gastro-enterostomy in 8 cases.

### CONCLUSIONS

1. An accurate diagnosis of a lesion in the upper urinary tract must be based on a detailed history, careful physical examination, complete laboratory studies of urine and blood, and a thorough urological study. Every pathological condition in the kidney and ureter should be studied not only from the standpoint of its effect upon the urinary tract but also upon the body as a whole.

2. Pathological conditions in the upper urinary tract usually are accompanied by well recognized symptoms complexes but occasionally are unaccompanied by any urinary symptoms. In many instances they produce symptoms referable to other organs or systems or organs outside of the urinary tract, particularly in the gastro-intestinal tract.

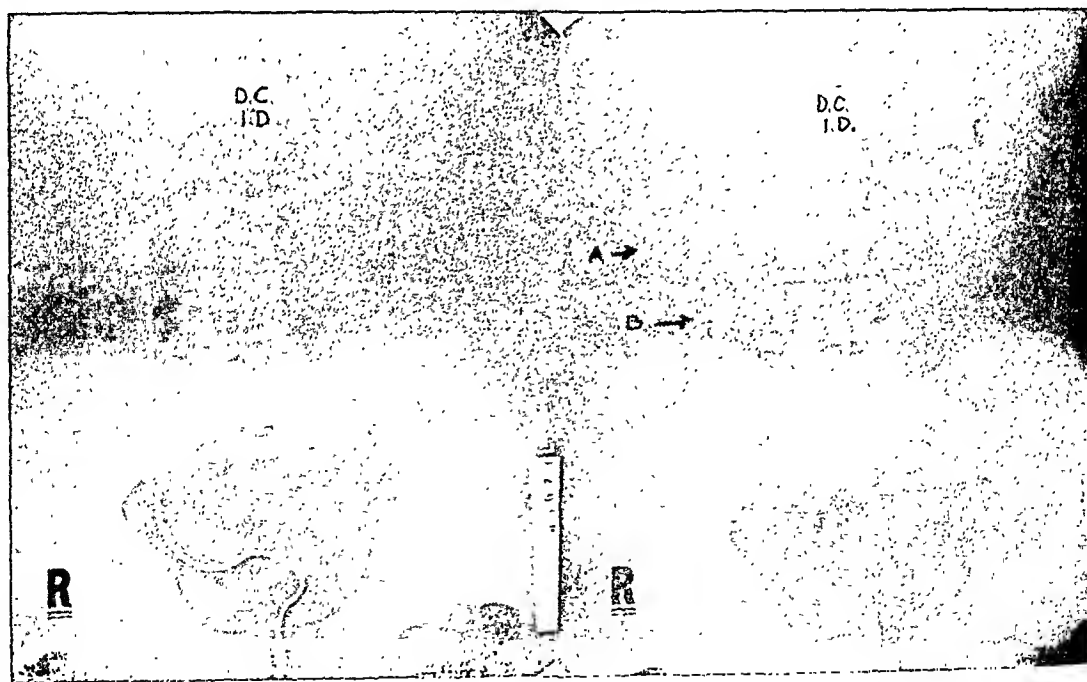


Fig. 11. Case 12: Roentgenograms in a case of concomitant ureteral and biliary lithiasis. On the left, the arrow (A) points to a group of 10 to 12 small round shadows in the gall bladder and the arrow (B) points to a large irregular calculus in right ureter. The pyelogram of the left kidney reveals a normal pelvis. On the right, the roentgenogram was taken following the injection of 40 c.c. of a pyelographic medium and shows a large pyonephrotic kidney. The large right ureteral calculus situated above the tip of ureteral catheter is partly obscured by the opaque medium in upper ureter.

3. The gastro-intestinal manifestations of diseases in the upper urinary tract may be classified as (a) toxic, (b) mechanical or (c) reflex. The toxic type is associated with an acute or chronic inflammatory or obstructive lesions of the kidney and is due to the reaction to bacterial toxins or increased amount of nitrogenous compounds in the blood (uremia). The mechanical symptoms are obstructive in character and are due to pressure upon or irritation of the posterior peritoneum and adjacent intra-abdominal organs by an enlarged kidney, renal tumor or by perirenal accumulation of pus, blood or urine. The reflex type represents the response of the gastro-intestinal tract to reflex stimuli originating in the upper urinary tract and is known as the retroperitoneal syndrome.

4. The reno-digestive reflexes concerned in the retroperitoneal syndrome are classified according to their effects upon the various portions of the gastro-intestinal tract: the principal types are the renogastric and reno-intestinal reflexes. These reflexes may be motor, secretory or vasomotor. They may be associated with each other or combined with cardiac, respiratory or vasomotor reflexes or occur simultaneously with other visceromotor reflexes.

5. The point of origin of the reno-digestive reflexes varies in the different clinical cases. The response to these stimuli varies in the same or different individuals.

6. Factors influencing the response to these reno-digestive reflexes are (a) summation of primary irritative stimuli, (b) sensitization of nerve centers, and (c) individual predisposition.

7. The gastro-intestinal manifestations of these reno-digestive reflexes may be classified as (a) gastroduodenal (dyspepsia, ulcer); (b) biliary (cholelithiasis, cholecystitis, hepatitis); (c) appendiceal (acute or chronic appendicitis); (d) colonic (ulcerative or spastic colitis); and (e) peritoneal (ileus, intestinal obstruction). Cases illustrating each type are presented by the Author.

8. A complete urological examination is indicated in every obscure abdominal condition especially in those patients who have been subjected to an abdominal operation without relief. Every urologist should familiarize himself with the symptomatology of pathological conditions in the gastro-intestinal tract. Every surgeon should recognize the fact that lesions of the upper urinary tract may produce symptoms of a pathologic condition in the gastro-intestinal tract, and *vice versa*.

9. Pyeloureterography, retrograde or intravenous, is of immeasurable value in the differential diagnosis of lesions within the upper urinary tract and in their differentiation from other pathological conditions in the gastro-intestinal tract and in other organs adjacent to the kidneys and ureters. A "flat" roentgenogram of the genito-urinary tract should be adopted as a routine diagnostic measure in every obscure abdominal condition, especially in cases of so-called chronic appendicitis. The roentgenologist should also take a similar plate before administering any of the opaque substances used to delineate the gastro-intestinal or biliary tract in order to avoid overshadowing any radiable shadows in the renal or ureteral regions. A negative roentgenogram of the genito-urinary tract does not exclude a disease of the kidney or ureter. Pyeloureterographic studies should include pictures taken in the horizontal and upright positions in order to rule out a movable kidney. Stereoscopic pyeloureterograms are of great value in determining the exact location and size of any abdominal mass and its relation or effect upon the upper urinary tract.

10. The Author urges the establishment of adequate follow-up system to determine the incidence of cures and failures in the operative treatment of abdominal conditions in view of the high percentage of failures to obtain relief of abdominal pain as reported in statistical studies of large series of abdominal operations.

## REFERENCES

1. Abeshouse, B. S.: Rupture of the kidney pelvis; review of the literature and report of three cases. *Southern Med. J.*, Mar., 1934; 27:238; *idem. S., G., and O.*, March, 1935; 60:710.
2. Adler-Racz, A. V.: Gastro-intestinal disturbances following renal operations. *Ztschr. f. Urol.*, 1929; 22:713.
3. Aglave, M. P.: Note sur la position du rein chez le jeune enfant par rapport à la crete iliaque et reflexions sur l'ectopie renale. *Bull. et mem. de la Soc. Anat. de Paris*, 1910; 85:595.
4. Albarran, R.: Ileus follow nephrolithotomy. *Traite d. med. oper. d. voies-urin.*, Paris, Masson et Cie., 1909; p. 167.
5. Alleman, R.: Gastro-intestinal syndrome in congenital hydronephrosis. *Ztschr. f. urol.*, 1931; 28:226.
6. Ammon, E. V.: Intestinal obstruction following a nephrectomy. *Zentralbl. f. chir.*, 1927; 48:3034.
7. Agnelli, O.: Nephro-enteric syndrome from unrecognized calculus of renal pelvis. *Gior. Med. dell. Alto. Adige*, Balzano, 1929; 1:4.
8. Beck, H. G.: The relation of urologic disease to internal medicine. *J. Urol.*, 1930; 23:247.
9. Berkman, J. M.: Hydronephrosis, perinephritic abscess and renal destruction with gastro-intestinal symptoms. *Proc. Staff Meet., Mayo Clinic*, Sept. 21, 1932; 7:553.
10. Blesh, A. L.: Diagnostic difficulties of the right abdomen. *Southwestern Med.*, Feb., 1925; 9:52.
11. Block, L.: Gastro-intestinal manifestations in diseases of the urinary tract. *Trans. Chicago Urol. Soc.*, 1931; 1:163.
12. Brown, G. E.; Eusterman, G. B.; Hartman, H. R., and Rowntree, L. G.: Toxic nephritis in pyloric and duodenal obstruction. *Arch. Int. Med.*, 1923; 32:425.
13. Caravan: Quoted by di Maio.
14. Carnot, P.: Le jeu du sphincter pylorique. *Arch. d. mal. de l'appar. digest.*, 1907; 1:651.
15. Cecil, A. B.: Abdominal pain in diseases of the kidney and ureter. *J. A. M. A.*, 1920; 75:1239.
16. Chaurand, A.: Co-existent renal and biliary lithiasis. *Presse. Therm. et Climat. Paris*, 1927; 68:305.
17. Chaurand, A., and Debray, M.: Reciprocal connection between renal and biliary lithiasis. *Presse Med.*, 1923; 33:129.
18. Clavel, C.: Peritoneal and gastro-intestinal syndromes in surgical diseases of the kidney. *These de Lyon.*, Camugli, 1929, Bose, Freres et Rion.
19. Clavel, C.: Peritoneal type of contusion of the kidney. *L'Urologie du Prat.*, Paris, July 10, 1930.
20. Clavel C.: Acute abdominal syndromes following extraperitoneal operations on the kidney. *Arch. des mal. des reins et des org. gen.-urin.*, Aug., 1930; 5:174.
21. Colne, G.: Lithiasis of right bladder and kidney as associated syndrome of right side of abdomen. *Arch. di radiol.*, March-April, 1933; 9:316.
22. Colby, P. H.: Kidney lesions as a cause of gastro-intestinal symptoms. *J. Urol.*, 1932; 28:419.
23. Connor, W. H.: Urology and its place in group medicine. *U. S. Navy Bull.*, 1920; 19:329.
24. Cooke, A. M.: Calcification of kidney in pyloric stenosis. *Quart. J. Med.*, Oct., 1932; 2:539.
25. Dannreuther, W. T.: Incidence and significance of urological symptoms in gynecological practice. *Am. J. Obst. and Gyn.*, 1924; 8:103.
26. Davis, E. G.: Duodeno-ureteral fistula of spontaneous origin. *J. A. M. A.*, 1918; 70:376.
27. Denechau, E., and Prier, P.: L'ileus reflexe au cours de la lithiase reno-ureterale. *Presse Med.*, Aug., 1930; 69:1153.
28. Desnos: Dens observations d'entremblement intestinal nerveux au cours de la colique nephritique. *Union. Med.*, April 5, 1887; 43:535.
29. Ducuing, J., and Giscard, J. B.: Ileus due to renal ptosis. *J. d'Urol.*, 1933; 35:193.
30. Duvergey, J.: Paralytic ileus following nephrectomy. *J. Urol.*, 1924; 17:413.
31. Eisenklam, D.: Subcapsular rupture of the kidney with secondary compression ileus in ascending colon; case. *Med. Klin.*, 1933; 29:1050.
32. Fagge, C. H.: Case of hydronephrosis. *Brit. J. Surg.*, 1933; 21:151.
33. Fenwick, F. C.: A case of jaundice due to floating kidney; lumbar fixation; recovery. *Lancet*, 1899; 2:1296.
34. Ferrannini, A.: Renal syndrome in hepatic cirrhosis. *Policlinico (sez. med.)*, Aug. 1, 1934; 41:445.
35. Friedenwald, J., and Morrison, S.: Relation between gastric and renal diseases; clinical observations. *J. A. M. A.*, 1932; 99:524.
36. Frugoni: Pseudo-ileus from ureteral calculus. *Policlinico*, 1919; 26:1255.
37. Graeme, P.: Urinary forms of retrocecal appendicitis. *Bull. Med. Paris*, Feb. 27, 1932; 46:156.



38. Gauthier, C., and Clavel, C.: L'hydronephrose a forme gastro-intestinale. *J. d'Urol.*, 1931; 30:370.
39. Gayet: Occlusion intestinale post-operaire chez les urinaires. *Lyon. Chir.*, Jan.-Feb., 1925; 22:96.
40. Gayet and Ricard: Mecn-uretere et lithine renale ayant donne lieu a des accidents repetes d'occlusion intestinale. *Lyon. Chir.*, 1926; p. 225.
41. Giuliani: Renal colic treated by ureteral catheterization; expulsion of calculus; associated intestinal syndrome. *Lyon. Med.*, May 31, 1931; p. 725.
42. Goldstein, A. E.: Gastro-intestinal symptoms in prostatism. *Med. Record*, Jan. 3, 1934; 39:13.
43. Goldstein, A. E., and McEee, T. J.: The importance of a urological examination in the differential diagnosis of abdominal conditions. *West Virginia Med. J.*, Aug., 1925; 21:417.
44. Gottstein: Peritonitis of renal origin. *Zentralbl. f. chir.*, 1930; 57:1876.
45. Grasmann, K.: Etiology of spontaneous extensive hemorrhage in bed of kidney. *Deutsch. Ztschr. f. chir.*, 1923; 178:416.
46. Greco, F.: Non-traumatic perirenal hematoma. *Arch. ital. di chir.*, 1925; 11:11.
47. Guyon, F.: Troubles digestifs dans les maladies du rein. Lecons Cliniques sur les maladies des voies urinaires. Bailliere et Fils Paris, 1903; 1:2, 2:230-240.
48. Hndt, L. L., and Rivers, A. B.: Toxic manifestations following alkaline treatment of peptic ulcer. *Arch. Int. Med.*, 1923; 31:171.
49. Hend, H.: A disturbance of sensation with special reference to pain of visceral disease. *Brain*, 1892; 15:1.
50. Helwig, F. C., and Schutz, C. B.: Liver-kidney syndrome; clinical, pathological and experimental studies. *S. G., and O.*, Nov., 1932; 55:570.
51. Hildinko, A., and Cano, F.: Paralytic ileus following nephropexy. *Revista espan. de chir. y urol.*, Feb., 1930; 1:13.
52. Higgins, C. C., and Hicken, H. F.: Spontaneous renal and ureteral fistulae. *Arch. Surg.*, 1933; 27:317.
53. Higgins, J. M.: Acute enterocolitis with perinephritic abscess. *Penn. Med. J.*, 1932; 35:707.
54. Huguler and Parvu: Sur un cas de spasme du transverse et du grele consecutif a un calcul du rein, et verifie par l'invention chirurgicale. *Medicine Moderne*, Feb., 1914; p. 5. Also Paris chir., 1913; p. 682.
55. Hunner, C. L.: End results of 100 cases of ureteral strictures. *Am. J. Obst. and Gyn.*, 1924; 8:793.
56. Iselin: Occlusion intestinale, par spasme, determinee par une colique nephritique, puis chez la meme malade par la pyelotomie. *J. d'Urol.*, 1924; 17:416.
57. Ismet: Chirurgische Klinik der Nierenkrankheiten. Berlin, 1901, Chnpter un Lithiasis; p. 283.
58. Jankelson, J. R.: Ureteral calculus simulating intestinal obstruction. *Med. J. and Rec.*, May 7, 1930; 131:468.
59. Kapel, O.: Peritonitis of renal origin. *Deutsche Ztschr. f. chir.*, 1923; 230:462.
60. Krecke, A.: Über die pathologie und diagnostik der erkrankungen des rechten oberbauchens. *Munch. Med. Wchnschr.*, Sept. 23, 1932; 79:1556.
61. Labnt, G.: Regional anesthesia. Phila. and London, 1923.
62. Laffer, W. B.: Acute dilatation of the stomach and arterio mesenteric ileus. *Ann. S.*, 1908; 47:532.
63. Lawrie, M.: A case in which movable kidney produced the usual symptoms of hepatic colic. *Brit. Med. J.*, 1901; 1:15.
64. Lebesconte, M.: L'ileus fonctionnel. *These Paris*, No. 304; 1913.
65. Legre, J. E.: A useful sign in the diagnosis of ureteral stricture and its sequelae. *J. A. M. A.*, 1916; 87:2113.
66. Legueu, F.: Des calculs du rein et de l'uretere. *These Paris*, 1891.
67. Legueu, F.: Sur la paralysie stomacale aigue post-operaire. *Bull. et Mem. Soc. de Chir. de Paris*, 1905; 31:974.
68. Lick, E.: Die nervose Darmposmus. Ein Beitrag zur differential diagnosis der appendicitis. *Munch. Med. Wchnschr.*, Dec. 25, 1917; p. 1659.
69. Lissowknja, S. N.: Sur les causes du meteorisme intestinal et de la dilatation aigue de l'estomac, apres les operation sur les reins. *Arch. des mal. des reins et des org. gen.-urin.*, Feb., 1928; 3:231.
70. Livingston, E. M.: Further studies of viscerosensory phenomena; acute cholelithiasis; acute nephrolithiasis. *J. A. M. A.*, May 10, 1924; 82:1495.
71. Loeper, M.: Les manifestations de la colique nephretique. Lecons de pathologie digestive; Masson, 1914; 3rd series, pp. 236 to 269.
72. Loring, I.: Acute abdominal syndrome. Right renal ptosis. *Revista de Urol. de Chile*, Aug., 1925; 1:5.
73. Lowale and Twelven: Quoted by Stevens.
74. MacLagan, T. J., and Treves, F.: Three cases in which movable kidney produced symptoms of gall stones. *Lancet*, 1900; 1:15.
75. McKeenzie, J.: Associated pain of visceral disease. *Med. Chronicle*, 1892; 16:295.
76. de Mino, G.: Gastro-intestinal and abdominal syndromes in this presence of surgical diseases of urinary tract. *Osp. Maggiore*, March, 1932; 20:133.
77. Maire: Difficulties du diagnostic des grosses hydrocephroses. *Theor Lyons*, 1909.
78. Mathe, C. P.: Spontaneous rupture of the kidney. *Urol and Cutan. Rev.*, 1932; 36:603.
79. McGlannon, A.: Intermittent hydronephrosis with gastro-enterologic symptoms. *Ann. Surg.*, 1922; 75:372.
80. Mitry: Anurie calculeuse et ileus reflexe gueris par la distension des bassinets. *J. d'Urol.*, Aug., 1925; 20:160.
81. Morrison, D. M.: Ureteric lesions as a cause of abdominal symptoms; a consideration of ureteritis or urethral stricture. *Nov.*, 1931; 38:153.
82. Nisio, G.: Renal enervation. *Arch. ital. di chir.*, 1927; 17:577.
83. Nisio, G.: Uronephrosis of right kidney simulating appendicitis and cholelithiasis; with report of six cases. *Policlinico (sez. prat.)*, Sept. 4, 1933; 40:1408.
84. Nogues: In discussion of Duverney's article.
85. Oudard: Paralytic ileus with aerophagy after nephrectomy for renal tuberculosis. *J. d'Urol.*, 1925; 20:506.
86. Ozeki, Y.: Duodenal stenosis due to arterio-mesenteric compression developing after pyelolithotomy. *Japan. J. Derm. and Urol.*, Feb., 1934; 35:20.
87. Page, K. B.: Renal stone in its relation to gastro-enterology. *Am. J. Gastro-Enterology*, 1911-1912; 1:13.
88. Papin, E.: Enervation du rein. *J. d'Urol.*, 1923; 16:296.
89. Petit-Deutails and Flandrin: Anatomie chirurgicale des nerfs du rein. *Soc. Anat. de Paris*, Oct. 27, 1923; pp. 635-647.
90. Plenz, P. G.: Über Beziehung zwischen niere senkung und magendarmnahrung. *Deutsch. med. Wchnschr.*, 1922; 48:1137.
91. Prieur, R.: Etude de l'ileus reflexe au cours de la lithiase ureterale. *These de Paris*, Oct., 1929.
92. Quenu: Symptoms of intestinal obstruction in renal colic. *Bull. med.*, March 5, 1913; 18:207, and March 8, 1913; 19:219.
93. Ramon: Renal colic. Lecons de clinique medecine pratique, 1926; 6th ed., edited by Vigot, p. 410.
94. Reynier and Lechevallier: Quoted by di Maio.
95. Rinaldi, R.: Reflex abdominal disturbances in urinary lithiasis. *Arch. ital. di Urol.*, 1929; 5:118.
96. Ritch: Quoted by Block.
97. Rohmer, P., and Tassovatz, T.: Significance of renal syndrome in acute dyspepsia of nurslings. *Bull. Soc. de Pediat. de Paris*, June, 1933; 31:296.
98. Rolleston, H., and McNee, J. W.: Diseases of the liver, gall bladder and bile ducts. McMillan Co., London, 1929; 3rd Ed., p. 584.
99. Ropke, W.: Unilateral kidney disease manifested as ileus. *Zentralbl. f. chir.*, 1933; 60:914.
100. Rost, F.: Perforation into the abdominal cavity of pus from a calculus kidney, case report. *Ztschr. f. urol.*, 1931; 25:439.
101. von Saar, C.: Ueber hydronephrosen ruptur an den dabil auftretenden symptomkomplex. *Beitr. z. Klin. chir.*, 1903; 64:336.
102. Samuels, A., and Kern, H.: Hydronephrosis with gastro-intestinal symptoms. *Urol and Cutan. Rev.*, 1926; 30:644.
103. Seze, S. de: The peritoneal and gastro-intestinal forms of renal lithiasis. *Progres. med.*, Dec., 1929; p. 2142.
104. Sherrin, J.: The diagnosis of gall stones. *Lancet*, 1911; 1:870.
105. Smith, E.: Gastro-intestinal symptoms in hydronephrosis and renal calculi. *Canad. Med. Ass. J.*, March, 1933; 28:281.
106. Sormani, P. P.: Syndrome of acute intestinal obstruction of colon in renal colic. *Rassegna di clin. Therap. e. Scinzaz, Affin.*, Rome, Nov.-Dec., 1931; 39:329.
107. Sternberg: Clinical study of renal calculi, particularly their gastro-intestinal manifestations. *Wien. Klin. Wchnschr.*, April 18, 1901; 14:381.
108. Stevens, W. E.: Upper urinary tract and the adjacent organs; the differential diagnosis of pathologic conditions. *California and Western Med.*, Sept., 1932; 37:160.
109. Stewart: Possible obscure diagnoses with renal calculi. *Am. J. Med. Sci.*, 1905; 130:227.
110. Stoenca, F.: Acute dilatation of the stomach following nephropexy. *Arch. ital. de Chir.*, 1924; 9:550.
111. Swann, C. S.: Gastro-intestinal symptoms from left renal tumor. Demonstration of metastases around the sympathetic nerves having renal and gastric associations. *New England J. Med.*, Feb. 15, 1934; 210:346.
112. Tassin: Occlusion intestinale survenue, chez la meme malade, apres chaque nephropexie pour double rein flottant. Quoted by J. Chardonnet: Contribution a l'etude de la nephropexie. *These Montpellier*, 1898; 64, p. 43.
113. Thevenard: Renal colic with symptoms of intestinal obstruction. *Soc. des Chir. de Paris*, July 11, 1913; Paris Chir., 1913; p. 702.
114. Thomas, J. E., and Wheelon, H.: The nervous control of the pyloric sphincter. *J. Lab. and Clin. Med.*, 1922; 7:375.
115. Tixier: Quoted by Tixier and Clavel.
116. Tixier, L.: L'hydronephrose en chirurgie generale. Vol. jubilaire de Forgue, Paris, Masson, Nov., 1924; p. 310.
117. Tixier, L., and Clavel, C.: Troubles gastro-intestinaux graves, causes par des calculs du rein et de l'uretere (discussion). *Lyon. Chir.*, May-June, 1931; 28:352.
118. Tixier, L., and Clavel, C.: The retroperitoneal syndrome and the relation between the kidney and gastro-intestinal reflexes. *S. G. O.*, 1932; 54:505.
119. Tucker, W. J.: Infections of the kidney. *Wisconsin Med. J.*, 1921; 20:277.
120. Uteuu: Two cases of post-operative paralytic ileus. *J. d'Urol.*, 1924; 17:533.
121. Vermooten, V., and McKeown, R. M.: Renocolic fistulae. *Am. J. Surg.*, 1933; 21:242.
122. Wharton, L. R.: The innervation of the ureter with respect to denervation. *J. Urol.*, 1932; 28:639.
123. White, W. H.: Cases of jaundice due to aneurysm of the hepatic artery and to movable kidney. *Brit. Med. J.*, 1892; 1:223.
124. Zeman, F. D., Friedman, W., and Mann, L. T.: Kidney changes in pyloric obstruction. *Proc. Soc. Exp. Biol. and Med.*, 1923-24; 21:179.
125. Zallocco, A.: Renal calculi with gastric syndrome. *Pediatrica*, Naples; 1929; 37:325.



## SECTION VIII—*Editorial*

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastroenterological Association is in no way responsible for editorial expressions.

### President's Address\*

By

B. B. VINCENT LYON, M.D.  
PHILADELPHIA, PENNSYLVANIA

IT is now thirty-eight years since this Association was founded. Under able leadership gradually it has risen to a position of very real influence, nationally and internationally, in the field of gastro-intestinal medicine and surgery.

It has been the custom to have the annual meeting opened by a Presidential Address. This year it becomes my high privilege to serve. I am fully conscious of the honor and of the dignity of the office to which you have elevated me and I desire to express my appreciation of your confidence and my hope that I may achieve a measure of that success accomplished by my predecessors in office.

In reviewing previous presidential addresses, one is struck by the fact that periodically they view with pride our past achievements, view with alarm our evident delinquencies, or, still again, paint the future of gastroenterology in rosy hues, in which, prophetically, our Association will play a leading rôle.

Let me attempt a brief mingling of the three. During the first ten years, our Founders devoted themselves chiefly to the problem of organizing this Association on a sound foundation by the establishment of it as a forum before which our members could annually exchange views which crystallized into new deeds with startling rapidity. Our Founders were, for the most part, original thinkers in advance of their day. They were pioneers and subsequently became stimulating teachers in their field. They were men of indefatigable energy and zealous in their effort that this Association should achieve distinction. Many of this small band of original members are dead; the majority who survive have reached the position of honor that our Senior membership group now enjoys. To these members, our Association—and medicine in the large sense—owes a debt without a moratorium.

During the second and third decades, our Association further was strengthened by certain changes in organization; by the creation of an Associate group of members constantly bringing in new blood, among whom will be found the brains of future leadership, and by the creation of that most necessary adjunct to progress our Research membership group—now small in number but each name of which adds lustre to our Association because of outstanding accomplishments.

Throughout this thirty year period there poured forth from the pens of our members hundreds of articles which helped to fill the pages of American and European medical journals, articles which stimulated and challenged the interest of internists and surgeons throughout the world, and which put gastroenterology on the map of medicine.

The historically inclined Hemmeter, in commemoration of our thirtieth anniversary, carefully reviewed them all and stated that, in his opinion, fifty-three of the contributions could be classed in the A or double A group—that is, publications that were pivotal, of exceptional merit and which sharply modified views previously held; or publications which were epochal, in creating an entirely new view of some aspect of digestive diseases, etiologic, diagnostic or therapeutic.

During this now closing fourth decade, our Association has made further progress. There is not time to go into details, but I will briefly allude to nine items of endeavor which I consider worthy of special mention. *First*, the discovery, by Ivy, of a new hormone which possesses the power to produce a contraction of the gall bladder, assisting its evacuation of bile. We are eagerly awaiting the "purification" of *cholecystokinin* to a degree sufficient for it to be safely used in human beings. It should be a great addition to our gall bladder therapy. *Second*, Alvarez' able discussion of functional gastrointestinal disease and the importance of its recognition and management as set forth in his book, "Nervous Indigestion." In my opinion, it is already a classic. *Third*, the discovery of a new clinical entity by Crohn and his associates, which has been called "Chronic Regional Ileitis" and which appears to be proved and accepted. *Fourth*, the excellent work of William H. Stewart in so greatly improving the technique of oral cholecystography by his "intensified" method. *Fifth*, the very intriguing new conception of Cole regarding the genesis and pathological sequence of gastric ulcer. To conceive of its starting as a mural rather than a mucosal lesion is most novel and revolutionary and is a testimonial to Gregory Cole as an original thinker. But it still remains to be proved, as do the *sixth* and *seventh* meritorious efforts, namely, Lay Martin's announcement of urease as a new component of gastric juice, and the views of our lately lamented Founder member, Willy Meyer, regarding

\*Presented before the 35th Annual Session of The American Gastroenterological Association, Atlantic City, N. J., June 10, 1935.

the etiology of cancer. Time alone will prove them right or wrong.

The *eighth* and *ninth achievements* are to be considered tactical rather than scientific, but are of great potential value to the future of our Association. I refer, first, to our completion last year of an affiliation with the "American Journal of Digestive Diseases and Nutrition" by which that periodical becomes the Official Journal of our Association. This is a great accomplishment, for it now gives us something which we have lacked and wished for these many years. In it will henceforth appear, as long as our agreement mutually is satisfactory, all papers and discussions presented and certified as meritorious by a Council at our Annual Meeting, together with a large number of articles from other authoritative sources. It should be a great help to students of this subject to find such a large percentage of the more important papers on gastroenterology published in one Journal, instead of scattered through several. Besides this, our Transactions will now be published at an annual saving to our Association of approximately five hundred dollars. This can go into our "war chest" to help out with the funding of purposes which may be suggested.

The *ninth achievement* consists of our attempt to set up a Board of Examiners properly to certify the qualifications of a candidate in becoming a Specialist in gastrointestinal medicine. This is of vital importance to our future. Unless we can define and prescribe what a student of gastrointestinal medicine *must do* and *must be* in order to be classed as a Specialist in this subject, then gastrointestinal medicine never will exist as a recognized specialty. However, it is well that we remember that the so-called "Stomach Specialist" who, because of inadequate training in the clinic, in the operating room, in the research, pathological or X-ray laboratories or in the autopsy room, practices his subject within too narrow limits: he himself becomes a menace both to his patients and to gastroenterology. The subject is so immense, so intimately interwoven with clinical medicine, surgery and neurology, that no one can become a really able gastroenterologist until he has first become a good medical clinician. These last two endeavors have required much individual and joint labor and the work is not yet finished.

Let me now allude to two additional thought-provoking objectives of this fourth decade. The first is the constructive criticism of Frank Smithies in his presidential address in 1929 in which he called our attention to the great necessity of establishing standards in gastroenterology, so that when any of us is discussing any special topic he may talk in language which is "standard" and recognized as such by all of us. Particularly important was his criticism of the present lack of any suitable "standard" for the truer understanding of the secretory mechanism of the stomach, and in pointing out that we might properly discard all of the carbohydrate test meals and substitute instead a suitable mixed test meal as a test of gastric function in which the stomach itself is more concerned.

Secondly, let me mention the excellent work begun by Aaron of Buffalo and his co-workers in connection with an attempt to standardize usefully workable tests for enzymes. Last year we heard and approved the preliminary report of this Committee and with an increased personnel this important study is being continued. Perhaps, I should, in this connection, call your

attention to David Riesman's suggestion on our 30th Anniversary, that more work is urgently required in regard to salivary digestion. All such constructive criticism should not be ignored for so many years but should encourage some of us to carry the idea to a conclusion.

Currently, there are some who say that the American Gastro-Enterological Association is nothing but a smug medical club and not representative in its subject. Much of such talk is loose. Our record speaks for itself. If there is a headache in such gossip I shall leave it to my successor to use his own brand of aspirin.

So much in retrospect. Now let me call to your attention the following things which I would like to see accomplished by our 40th Anniversary, two years hence.

First, that our Active and Associate membership quotas of a hundred members and twenty-five members respectively should be *filled*, and a waiting list for each created. Thereafter membership in our Association will be coveted even more than now.

Furthermore, since our present financial security now depends wholly upon our membership dues and since each year a larger number are admitted to Senior membership, exempt from dues, a full list of Active and Associate members would yield a revenue which might permit us to create funds for special purposes. Among such might be a prize or medal for the best paper at each annual meeting—awarded either by membership vote or committee selection; funds to create additional lectureships similar to the Alvarez Lecture so generously founded by Smithies in 1929; or funds that could be devoted partly or wholly to defraying the expenses of guest speakers. The annual saving, now made possible by the publication of our Transactions, might be devoted in part to these purposes. But, in the effort to fill our Active and Associate memberships, our Committee on Admissions and Ethics and our Executive Council should exercise extreme care that only the most meritorious candidates be given consideration: candidates who are gentlemen in medicine, imbued with the highest respect for the ethics, the altruism and the scientific accuracy of our honorable and honored profession.

Secondly, I should like to see a change in our Constitution, which now prescribes the publication of papers sufficient in number and in merit as a condition of membership but which will not automatically debar an otherwise outstanding candidate. I can think of several men who are good clinicians, keenly interested in gastroenterology, who each year attend our meetings as observers. These men are wide awake, often capable teachers and are men who would become valuable and enthusiastic members. But, because they are not gifted in writing, these men, by Article II of our Constitution, are now debarred from membership. In my opinion this is wrong. Too often a native fluidity of pen is accompanied by a paucity or vacuity of ideas. As a result, such a candidate is eligible for election and is not infrequently elected. Such men weaken rather than strengthen the prestige of our Association. Of course, the man who genuinely contributes to the literature of gastroenterology advances the progress of our profession and should always be given the preference, but I feel that the otherwise capable clinician, although not gifted in writing his thoughts, should not thereby be considered non-eligible for membership.

In the third place, I should like to see our Research membership, now nearly wholly limited to physiologists, enlarged and strengthened by the election of carefully selected representatives from surgery, pathology, bacteriology, chemistry, biochemistry and toxicology. These men should be—like our physiologists—of national or international reputation and should preferably be under forty-five years of age. What help such authoritative experts could be to us in clarifying our too often muddled views; in more quickly settling our sometimes discordant squabbles; in keeping our feet on solid ground and out of the quicksands of immature speculation which provokes discussions lasting many years, to no purpose except delaying real progress; and lastly, to help us in the development of the project to which I shall soon refer!

In the fourth place, I should like to see our Annual Meeting extended to a three day session, one of which should be devoted to an open forum or round table discussion. Here, as many members as are interested, can "talk it out," can plumb one another's deepest views and ideas, and can have a real opportunity to sift wheat from chaff. What a help that would be! It could be carried on in large groups or in small; men discussing quite informally topics of diagnosis, treatment or research in which they are mutually interested. I am sure—and I know it has been a pet idea of John Bryant and of Walter Alvarez—that such a day would be the most worthwhile of all and the most productive stimulus to each member's next year's work. With our present two day session, which now must be limited to twenty-four papers and run off with impartial precision within the time limits allotted, I often leave a meeting vainly regretting that I had no time to see "So and So" and learn at first hand more of the things we have corresponded about, or that I think he may have "up his sleeve" and is willing and anxious to discuss. But alas, the official program is finished and men are hurrying to pack up and catch trains and the opportunity is lost. For our mid-western and far-western Fellows, a third day, devoid of tiresome papers, but devoted to informal discussions and establishing of closer personal contacts would make the long trip worthwhile. And in the spirit of mutual fairness, I should like to see our Annual Meeting held every third or fifth year in some southern, midwestern, or Canadian city.

These four wishes of mine already are shared by many of our members and can readily be translated into action if they meet with your approval, although one of them will require an amendment to our Constitution.

And lastly, I come to the fifth wish that might be achieved before our Fortieth Anniversary. It is a much larger project but one of vital importance to our Association as a whole and to each and every member of it. It is not impossible to achieve but it will require a united campaign and much hard work. I am convinced that it is a goal worth striving for, and, if and when created, will greatly accelerate the progress of medicine.

But before I state the project, may I ask you a question? Why is it that despite the individual and collective energy, the soul-absorbing work of so many members; despite their many meritorious contributions to medicine, nevertheless such epoch-making discoveries as insulin in diabetes; such as liver extract, ventriculin and addisin in pernicious anemia, as recent ex-

amples, have been the brain-children of research workers or clinicians outside of our membership. What is wrong with us? Haven't we the brains? Yes, we have the brains but what we lack is organization and often the opportunity to work.

*What we need is a Research Institute!* An institute promoted and controlled by ourselves, and devoted solely to solving problems in gastroenterology and metabolism. What we need is *The American Research Institute of Gastro-Enterology!* Think of it, gentlemen, there is no such institute anywhere in the world today. That has been our trouble; not lack of brains but lack of organization and opportunity.

Our trouble has been that when a member in San Francisco, or in Boston, in New Orleans or in Canada, in Chicago, New York, Baltimore or Philadelphia, gets a bright idea, wants to put it to work, to engage in a research, he is handicapped from the start. It is all right for the little problem but not for the big one. Members of this Association from the Mayo Clinic are the only exception. Review the number and merit of the papers they have contributed and you have the answer. Organization through all departments! Few of the rest of us have sufficient gastrointestinal beds and we are too frequently handicapped by the lack of interest, by the indifference or perhaps by the jealous or personal animosities of the heads of other staffs or departments. And so often we are handicapped for lack of funds.

Unusual as it may sound, I fully believe that a wide-awake clinician, cognizant of the deficiencies of our diagnostic and therapeutic knowledge and possessed of the inquisitive rather than the acquisitive mind, might, with the help of the scientific laboratory research-man, prove to be a reliable, perhaps brilliant research worker. It would be most timely, if we pooled our resources, our brains, our energies, our experimental and practical equipment. *Wherefore* the Research Institute.

If such an Institute were founded, I would make the following suggestions: First, that it should be incorporated and placed under the wing of an accredited Class A medical school in a Class A medical center. This should, to some extent, be left to the wishes of the donor of the Institute. Likewise, its name. But the controlling influence in its policy should be under the supervision of the American Gastro-Enterological Association.

Second, that its Foundation should be properly trusted and with a suitable Board of Directors.

Third, when such an Institute has been founded, that our Association should be empowered to make selection of its major operating personnel: A Clinical Director of Research and a Laboratory Director of Research, or combine the two offices, and hold him or them responsible for the selection of suitable assistants. Such assistants should consist of Chiefs of seven laboratories, (1) general; (2) physiology; (3) pathology; (4) bacteriology; (5) chemistry and toxicology; (6) X-ray, and (7) animal, utilizable by all laboratories under direction; a Business Manager and a Directress of Nurses. Such Chiefs of Department should be experienced men or women and should be allowed to select their co-workers. Among such should be included suitable Fellows, provided by the Foundation, to work on problems in physiology, pathology, bacteriology and chemistry.

Fourth, that in addition to this active personnel of the Institute itself, there should be created two co-

ordinating committees; a local committee, consisting of the heads or suitable members of the various Professional Departments in the Medical School under the wing of which the Institute itself is housed and a National Advisory Committee consisting of acknowledged experts in clinical or research medicine or surgery and in gastro-enterology who should be selected and requested to serve.

Fifth, such an Institute should have a minimum of forty ward beds and twenty private beds devoted exclusively to gastrointestinal problem cases. This is a bare outline of the major requirements. The details are too many to allow of discussion.

Sixth, when we get such an Institute, how do we put it to work? My suggestion would be that before each annual meeting, our Secretary should send out a questionnaire to members requesting information regarding particular research they have in mind. Our Council shall then tabulate it for a vote at each annual Executive Session for the selection of an annual "key problem" and two or more correlated problems. The matter then should go before the Director of Research and his Chiefs of Departments, assisted by the National Advisory Committee, for thorough study of the best way to approach the research in order to carry it to a successful conclusion. Thus we concentrate all our resources on one selected problem; and we pool our brains, our eyes, our ears, our hands and our imaginations. If the research is brought to a successful conclusion and any new discovery thereby announced, the individual whose idea originated the research should be then given a full share of credit.

We must find some way to solve the liver-spleen group of diseases; the severe bowel diseases whether of the peptic ulcer type or ulcerative colitis. We have none of the final answers now but we will have. And many other pivotal researches await us.

My own opinion is that the liver is the first "key problem" we should attack. I should like to see a con-

centrated effort made to study two greatly neglected functions of the liver, its detoxifying ability and its bactericidal power. What a field that one research would open up for profitable study! What a brilliant light it might throw on many clinical problems which now baffle us, such as the recognition of the cirrhoses before the decompensation stage; the large group of hepatic-intestinal toxemias; the migraines; the arthritides with gastrointestinal symptoms or with allergy; the toxemias of pregnancy; the pseudo-epileptics or epileptoids; the psycho-depressives; certain of the blood dyscrasias—to mention just a few problem groups so frequently seen by all of us. For years I have become convinced that faulty detoxifying or bactericidal power of the liver is intimately related both to the etiology and symptom-complex of these groups. This research, on a broad scale, must be undertaken. But this is not the time or place to give the details as to how it might be approached.

And I should like to see a study designed to explain what there is in the *succus entericus* or *enterokinase* that appears to protect against cancer those intestinal segments lying between the pylorus and the cecum. Within that area of the gastrointestinal tract cancer is relatively rare, whereas elsewhere it is common.

But gentlemen, we haven't yet got our Institute beyond a dream on paper. How shall we get it in fact? We must at once bend all of our energies and our abilities as *salesmen* to find a suitable donor and sell him the idea. There must be someone still possessed of a million or more to start such a Foundation. If any of us know of any candidate whom we might thus honor, as Rockefeller, Carnegie, Phipps and others have been honored, make his name known to us! There should be enough prestige for scientific effort and altruism among our combined membership to make him feel the need of our urgings and create for us a Foundation for such an organized effort in the interests of suffering humanity.

## ABSTRACTS

PAINE, JNO. R.

*The History of the Invention and Development of the Stomach and Duodenal Tubes. Ann. Int. Med., VIII, 752, December, 1934.*

The physician who finds interest in Medical history will read the original paper, though more than a mere historical sketch is found in its subject matter. Some attention is given to the clinical use of both the gastric and duodenal tubes, even to description of technique. The paper does not lend itself to abstracting very satisfactorily, since its chronological references are already compact. The origin of the stomach tube is said to be coeval with the Christian era, though credit is given to John Hunter for first recording its use 1790 years later, but Munro claims it for his father, who is said to have used such a tube as early as 1767. Hunter's description of his tube appeared in the Philosophical Transactions in 1776, just about four months before the Declaration of Independence by the American Colonies. It was made of eelskin, sponges, blad-

der, a wooden pipe, all drawn over a probang. From 1800 to 1822 the tube was variously modified and improved in England, France and the United States. In this country it appears that one, Physick of Philadelphia, used urethral catheters for lavaging the stomachs of infants. Strangely, its use was almost forgotten until made popular by Kussmaul about the close of the Civil War in 1865.

The duodenal tube is not of such ancient lineage and claims America as its birthplace. Crude tubes and unsatisfactory use were reported in 1894 by Turk, but fifteen years elapsed before really satisfactory clinical use of such a tube was obtained by Gross and Einhorn almost simultaneously. In 1912 Hess removed duodenal contents from infants with a Nelaton catheter and in 1921 the most satisfactory tube perfected, even to the present time, was described by Levin. The duodenal tube has been used by surgeons as a therapeutic measure since Westermann's report in 1910 and surgeons now use such a tube more frequently, perhaps, than internists.

Virgil E. Simpson, Louisville.

## SECTION X—After “Hours”

### Members of the Journal's Editorial Council Receive High Honors

**A**T the 1935 Annual Session of The American Medical Association held at Atlantic City, New Jersey, by vote of the House of Delegates two distinguished members of this periodical's Editorial Council were elected to the highest honors within the gift of the Association.

Dr. James Tate Mason, Seattle, Washington, nationally and internationally known surgeon, was chosen President-elect and Dr. Kenneth Merrill Lynch, Professor of Pathology and Vice Dean of the Medical College of the State of South Carolina, recognized throughout the world for his researches in Pathology, particularly human parasitology, was made Vice-President-elect.

Seldom has such outstanding recognition simultaneously come to the members of an editorial staff of the same publication. That the honor is well-deserved, amply is demonstrated by the biographical sketches of our co-workers as set forth below.

The Editors, their fellow-members of the Editorial Council and the Publishers of the Journal extend most cordial congratulations to Drs. Mason and Lynch. The American Medical Association, indeed is fortunate in being able to look forward to having at its head men of such outstanding scientific and personal merit.

#### JAMES TATE MASON, M.D.

Dr. James Tate Mason was born at Lahore, Orange County, Virginia, on May 20, 1882. His grandfather, Capt. Claiborne Rice Mason, was one of “Stonewall” Jackson's engineers during the Civil War. He was instrumental in building the old Virginia Midland Railroad and was the contractor who constructed the greater part of the Chesapeake and Ohio. Dr. Mason's father, Dr. Claiborne Rice Mason, also served under “Stonewall” Jackson until wounded and taken to Elmira, where he was kept as a war prisoner until the surrender at Appomattox in 1865. He became a student at the University of Virginia, and later graduated in medicine at Jefferson College Medical School at Philadelphia. Dr. Mason's mother was Mary Moore Woolfalk, born, reared, and lived all her life in Orange County, Virginia, and member of a family prominent from colonial times.

Dr. Mason went to the Locustdale Military Academy when he was 14 years of age, remaining there until 1901, when he entered the University of Virginia Medical Department, graduating in 1905.

Between 1898 and 1904 he served during the summer months as assistant to Col. James A. Frasier, who was owner and manager of the Rockbridge Alum Springs. He entertained his mother and father here for a few weeks every summer. There were no vacations between school attendance and the hotel management.

In the spring of 1905 Dr. Mason graduated in medicine at the University of Virginia. Immediately taking the Virginia State Medical Board in Richmond, he began his two year internship in the Philadelphia Polyclinic Hospital at 18th and Lombard Streets, which is now known as the post-graduate school of the University of Pennsylvania. Following this internship, he



James Tate Mason, M.D., Member of the Journal's Council, Chief Surgeon and President of the Virginia Mason Hospital and Clinic, Seattle, Washington. President-Elect of The American Medical Association.

had a residency at the Municipal Hospital of Philadelphia for the Treatment of Contagious Diseases.

In the spring of 1907 the Pacific Coast Steamship Company built two ships at the New York Shipbuilding Yards in Camden, N. J. To the first of these ships, the “President,” Dr. Mason became ship's surgeon. The ship went through the Straits of Magellan and finally arrived in Seattle in the summer of the same year. Two weeks after his arrival in Seattle, he accepted a position as local surgeon of the Pacific

Coast Coal Company, whose mines were at Franklin and Black Diamond. There he spent two years actively engaged in the practice of medicine and surgery, looking after the miners of the two camps, returning to Seattle in 1909.

In 1909 the late Robert T. Hodge, sheriff of King County, and the county commissioners of the time had a terrific political battle as to who would be responsible for the health of the prisoners. Following a court decision in his favor, the sheriff immediately placed his family and personal physician, Dr. Mason, in charge of the health of the prisoners, both those of the United States government, and those of the local government. In 1911 Dr. Mason was made coroner of King County and performed medical investigations for the county for four years. In 1914 he was appointed Superintendent and Chief Surgeon of the King County Hospital, a position which, with his private practice, he held until 1920.

In 1918 Dr. Mason and his associates organized the Mason Clinic, and in 1919 built the Virginia Mason Hospital, in which he has been Chief Surgeon and President of the Hospital Association for the past fifteen years.

He married Laura DeWolfe Whittlesey of Seattle, on January 3, 1912. His children are James Tate Mason, Mary Virginia Mason, and Frederiek DeWolfe Mason.

Dr. Mason is at the present time Consulting Surgeon to the U. S. Marine Hospital; Consulting Surgeon to the American Mail Line, the Alaska Steamship Line, and the Northern Pacific Railway Company; Fellow of the American College of Surgeons; member of the American Surgical Association, the Western Surgical Association, North Pacific Surgical Association, Washington State Medical Association, and the King County Medical Society; he was President, in 1931, of the Pacific Coast Surgical Association; President in 1930 of the American Association for the Study of Goiter. He is a past President of the Seattle Chapter of the Sons of the American Revolution, a member of Nu Sigma Nu, and Phi Gamma Delta. He is also a member of the Rainier Club, the University Club, and the Seattle Golf Club. His home is at 1220 Federal Avenue; his offices in the Virginia Mason Hospital.

#### KENNETH MERRILL LYNCH, M.D., LL.D.

Biographical notes based upon record in  
"Who's Who" in America

Kenneth Merrill Lynch, M.D., LL.D. Born Nov. 27, 1887, Hamilton, Texas. Married 1914. Two children. Member of the Episcopal Church. Educated in the public schools and the University of Texas, M.D., 1910. LL.D. (Hon.) University of S. C., 1930.

Resident Pathologist, Philadelphia General Hospital, 1911. Instructor in Pathology, University of Pennsylvania, and Assistant Pathologist to the Philadelphia General Hospital and the Hospital of the University of Pennsylvania, 1911-'13.

Professor of Pathology and Vice-Dean, Medical College of the State of South Carolina, Pathologist to the Roper Hospital, Charleston, and Consulting Pathologist to various hospitals in South Carolina, 1913-'21 and 1926 to the present. In private practice 1921-'26. Captain, M.C., U.S. Army, 1918. Member (or Fellow) of American College of Physicians, American Assoc. of Pathologists and Bacteriologists, American Society

for Cancer Research, American Society of Tropical Medicine, American Society of Clinical Pathologists, American Assoc. for the Advancement of Science, American Medical Assoc., American Society of Parasitologists, Alpha Omega Alpha, and other scientific and medical societies, having served in official capacity as follows:

Secretary, Medical Section, Pan-American Medical Congress, 1915; Secretary (1920 and 1928-'31) and Chairman (1932) Southern Conference on Medical Education; Secretary (1923) Vice-Chairman (1924) and Chairman (1925) Section on Pathology, Southern



Kenneth Merrill Lynch, M.D., LL.D. (Hon.) Member of the Journal's council. Professor of Pathology and Vice Dean Medical College of the State of South Carolina. Vice-President-Elect of The American Medical Association.

Medical Association; Vice-Chairman (1923) and Chairman (1924) Section on Pathology, American Medical Association; Board of Governors, American College of Physicians (1925-'27); Councillor (1922-'27) Vice-President (1928-'29) and President (1929-'30) American Society of Tropical Medicine; President (1930-'31) and Member of Executive Board (1931-) American Society of Clinical Pathologists; President (1930-'31) South Carolina Medical Association; Vice-President elect American Medical Association (1935-'36).

Research Medal, Southern Medical Association, 1921. Gold Medal Scientific Exhibit, American Medical Association, 1921; Honorable Mention, 1922. First Award, Scientific Exhibit, Southern Medical Association, 1920.

Member of National Board of Medical Examiners. Member S. C. State Board of Health, Member of the



Editorial Boards of the American Journal of Tropical Medicine, the American Journal of Clinical Pathology and the American Journal of Digestive Diseases and Nutrition.

Professor Lynch has made many notable contributions to the literature of his specialty. In addition to the authorship of two well-known text books ("Protozoan Parasitism of the Alimentary Tract," The Macmillan Co., N. Y., 1930, and—with H. W. C. Vines—the revision and editing of "Green's Manual of Pathology," Balliere, Tindall & Cox, London, and Wm. Wood & Co., Baltimore, 1934). Professor Lynch is a collaborator in "Approved Laboratory Technic" (Kolmer & Boerner), D. Appleton & Co., Philadelphia, and the author of more than 75 scientific monographs, the

major portion of which are concerned with original investigations in the field of human protozoiasis. Prof. Lynch was honored by being selected as one of six recognized authorities who brought practically before our profession the significance of intestinal amebiasis at the important Symposium arranged by the Council on Scientific Assembly of The American Medical Association at its 1934, Cleveland, Ohio, annual convention. Prof. Lynch's contribution to that Symposium was widely and most favorably commented upon.

Since assuming his duties at the University of South Carolina, Prof. Lynch already has published several investigations of outstanding value. He gives promise of steadily advancing the unusually solid and progressive standing of that well-known Institution.

## ABSTRACTS

DR. CHARLES H. FRAZIER AND DR. WILLIAM H. ERE.

*The Superior Laryngeal Nerve and the Superior Pole In Thyroidectomies. Annals of Surgery, Vol. 101, No. 6, June, 1935.*

The authors point out the fact that the treatment of thyrotoxicosis has shown great improvement in the past few years by the accepted agencies; medicinal, the Roentgen Ray, and surgery of which the latter gives eminent satisfaction at present. The authors prophecy, however, that, "In the course of time a new remedy be forthcoming, a specific, an organic compound which will provide the economy with what it needs and arrest this hyperplastic process."

Having reduced the operative hazards to a minimum, the mortality rate for toxic goitre in a well organized clinic, now being from 1 to 3 per cent, we should turn our attention to the elimination of post-operative discomforts such as accumulations of mucus in the trachea, frequent short coughs, efforts at expectoration which are painful, pain on swallowing, and various reflex pains.

Many of the postoperative discomforts, the authors state, are due to injury to the superior laryngeal nerves causing anesthesia of the larynx and the region of the epiglottis. Loss of sensation here abolishes the cough reflex, hence mucus accumulations. The troublesome little abortive cough or "hacking" was an ineffective attempt on the part of the patients to rid themselves of this accumulated mucus. The discomfort and pain on swallowing is due to injury to the constrictor muscles of the pharynx during operation—the inferior constrictor muscle being the one exposed during thyroidectomy.

In their experience, ligation of the vessels of the superior pole without injury to the external or internal branch of the superior laryngeal nerve is possible by avoiding traction or rough manipulation of the pole itself or the structures to the inner side of it. Then with adequate exposure dissecting the superficial flap of skin and platysma at least to the upper level of the thyroid cartilage, and then bisecting the ribbon muscles on one side or the other, with wide retraction of the wound edges, when the pole is clearly in view, Doctor Frazier divides this reflection of the pre-tracheal fascia either by blunt or sharp dissection. In the trough between these two walls of fascia lie the superior thyroid artery and vein and these may be tied either together or separately, thus both branches of the superior laryngeal nerve escape injury.

Charles T. Sturgeon, Los Angeles.

HUNT, VERNE C.

*Operability of Carcinoma of the Stomach. Annals of Surgery, Vol. 101, No. 5, May, 1935.*

The author gives a brief review of the operability and mortality rates of carcinoma of the stomach as found in the literature and in his series of 149 cases. He states that the relatively high inoperability should not obscure the benefits of resection in the truly operable tumors.

He attributes the low operability rate partially to the fact that early carcinoma rarely produces signs and symptoms or produces signs and symptoms of so mild a nature as to pass unnoticed until the tumor has metastasized and become inoperable. Inoperability may often be determined by clinical manifestations at the time of the initial examination; as the firm, fixed, sentinel gland in the left supra-clavicular space, infiltration of the umbilicus, the irregular, firm, nodular rectal shelf, an enlarged hard nodular liver, associated jaundice or ascites. By the foregoing determinations clinical inoperability has been in excess of 50% of all cases of carcinoma of the stomach. In the author's series of 149 cases the operability in terms of resection was 36.1% previous to 1930 and 36.8% during the past four years.

The author attributes the lowering of the mortality rate for gastric resection in the past few years to a great extent to the employment of methods during recent years for the rehabilitation of patients with carcinoma of the stomach previous to surgical exploration such as repeated gastric lavage for gastric retention, intensive administration of physiological solution of sodium chloride and glucose and the preoperative treatment of secondary anemia by blood transfusions.

In speaking of prognosis following gastric resection the author gives Grays statistics on a series of 373 cases. In 100 cases the patients did not survive longer than 12 months after operation; in 145 cases 12 patients had lived more than 5 years; and in 128 cases the patient had lived longer than 10 years. Gatewood, in 1932, stated that 46.1 per cent of patients who survived the operation lived more than 3 years, and 39.5 per cent survived more than 5 years.

In conclusion the author states that, "One opportunity exists to increase the curability of this disease and it is probable that this will come about through its earlier recognition and not through extension of operability, through higher gastric resection or total gastroectomy."

Charles T. Sturgeon, Los Angeles.

## SECTION XI—*Societies, Programs and Proceedings*

### IN MEMORIAM

#### Albert Bernheim

By

DAVID RIESMAN  
PHILADELPHIA, PENNSYLVANIA

**I**N 1896, Albert Bernheim emigrated to this country from the beautiful Black Forest region of Germany and settled in Paducah, Kentucky.

Although Dr. Bernheim had a degree in medicine from the University of Freiburg, he took a course in the Medical School of the University of Louisville and was graduated from that institution in 1897. After practicing for a brief period in Paducah, Bernheim came to Philadelphia. He soon acquired a good clientele and rapidly achieved a high degree of popularity in the profession, being elected, in 1905, President of the Northern Medical Association, the second oldest medical society in Philadelphia. He was keenly interested in gastro-enterology and was one of the first to practice that specialty in Philadelphia, being preceded only, I believe, by the late Dr. D. D. Stewart.

Although Dr. Bernheim was a faithful attendant at the meetings of the American Gastro-Enterological Association, to which he had been elected in 1909, he rarely took an active part in the proceedings, but his kindly and pleasant personality made for him many friends among his contemporaries in the Association.

In 1907 he published an English translation of Boas' book, "Diseases of the Stomach."

Fate dealt Bernheim a cruel blow. Just when the success to which his talents and industry entitled him was within his grasp, he began to show symptoms of paralysis agitans. After a brief but brave fight against that most terrible of maladies, he was forced to the wall and had to give up all medical work. Being a bachelor the doctor sought seclusion and sympathy in the home of a sister. After the death of this devoted relative and the dissipation of his small capital, he entered an institution for chronic invalids where he died on February 15, 1935. Death came in an access of hyperpyrexia, the temperature rising to 108° F. Among Dr. Bernheim's surviving relatives is a nephew, Julius Bloch, a contemporary American painter of note.

Albert Bernheim never spoke ill of anyone and those who knew him never spoke ill of him.

\*Presented at the 38th Annual Session of The American Gastro-Enterological Association, Atlantic City, N. J., June 10, 1935.

DELEGATES ON THE PART OF THE UNITED  
STATES TO THE FIRST INTERNATIONAL  
CONGRESS OF GASTRO-ENTEROLOGY  
APPOINTED BY THE DEPARTMENT OF STATE,  
UNITED STATES GOVERNMENT  
Brussels, Belgium, August 8 to 10th, 1935

Lieutenant Colonel John H. Trinder, Chairman,  
Medical Corps, Retired, United States Army.

Dr. Henry L. Bockus, 250 South 18th Street, Philadelphia, Pennsylvania.

Dr. Russell S. Boles, Rittenhouse-Plaza, Philadelphia, Pennsylvania.

Dr. Max Einhorn, 20 East Sixty-third Street, New York, New York.

Dr. Sara Jordan, 605 Commonwealth Avenue, Boston, Massachusetts.

Dr. B. B. V. Lyon, 2031 Locust Street, Philadelphia, Pennsylvania.

Dr. William Gerry Morgan, 1801 Eye Street, Washington, D. C.

Dr. De Witt Stetten, 850 Park Avenue, New York, New York.

Dr. Franklin W. White, 322 Marlboro Street, Boston, Massachusetts.



## UNDER PAR?

**S**ICKLY, undernourished and therefore frequently subnormal children usually present a difficult nutritional problem. Appetite is often poor or precarious, digestion often impaired, their tastes finicky.

Ovaltine has frequently been found of great assistance in this type of case, in helping to safeguard against child malnutrition by supplementing valuable proteins, carbohydrates, fats, minerals and vitamins in a palatable, easily digested form.

Ovaltine is a good source of the growth-promoting vitamins A, B and C, and an excellent source of the antirachitic vitamin D.

Ovaltine greatly increases the nutritive value of milk and makes it much more easily digested by its softening action on the milk curd.

During convalescence following debilitating diseases or operation, Ovaltine adds food quality to the diet. When given as a warm drink before retiring, it often induces sound, refreshing sleep without the aid of hypnotic drugs.

**This offer is limited only to practicing physicians, dentists, nurses and dietitians**

THE WANDER COMPANY

180 No. Michigan Avenue  
Chicago, Ill.

Dept: D. N. 10

Please send me, without charge, a regular size package of Ovaltine. Evidence of my professional standing is enclosed.

Dr. ....

Address .....

City ..... State .....

Canadian subscribers should address coupons to  
A. Wander, Ltd., Elmwood Park, Peterborough, Ont.

### Fill in the Coupon for Professional Sample

*Why not let us send you a trial supply of Ovaltine? If you are a physician, dentist, nurse or dietitian, you are entitled to a regular package. Send coupon together with your card, letterhead or other indication of your professional standing.*

# OVALTINE

*The Swiss Food-Drink*

*Manufactured under license in U.S.A.  
according to original Swiss formula*

## SECTION XII—"The Clinic"

### Bilateral Massive Suprarenal Hemorrhage in an Instance of Hyperfunction of the Suprarenal Cortex\*

By

FRANK R. FINNEGAN, M.D.  
ST. LOUIS, MISSOURI

**S**UPRARENAL hemorrhage has been reported numbers of times in medical literature (1). The largest number of cases reported was in infants from two to twenty-four months, a few cases in children up to eight years; in adults, the majority of cases was between twenty and thirty-five years—several above fifty years—divided about equally between the sexes.

A certain symptomatology, physical findings and clinical course was more or less common to all cases reported.

The onset was very acute in the majority of patients. A few cases were preceded by a general three to four day malaise. Then appeared severe pain either in the abdomen or lumbar regions, skin purpurae, nausea and vomiting, fever, signs of circulatory collapse, rapid fall in blood pressure, rapid pulse, frequent respiration, hypothermia, cold sweats, coma and death. According to Rabinowitz (2), an acute illness in a previously healthy child, which is rapidly followed by purpura and collapse, should, in the absence of a meningococcic infection, be sufficient for a diagnosis of suprarenal hemorrhage.

The etiological factor or factors of suprarenal hemorrhage have not been definitely proven. Some investigators believe it is due to a single organism, perhaps a streptococcus, but in the cases reported several different organisms have been found. Other investigators favor some form of in-

toxiation, either toxins or endotoxins of bacterial origin or autogenous poisons, for example: those that might be produced in the gastrointestinal tract. Infarction, from any of many causes, may be a common mechanism leading to the bleeding.

#### CASE REPORT

The patient, a married woman, aged 35. Mother of two children (normal

## Announcement Available for Treatment in PEPTIC ULCER

A recent paper in the American Journal of Digestive Diseases and Nutrition\* referred to a specially prepared colloidal Cream of Aluminum Hydroxide. These investigators reported that out of 110 cases with positive findings of peptic ulcer, excellent results were attained in 101, or 92%. We are pleased to announce that this preparation is now available to the medical profession under the convenient name of

*Creamalin*

In collaboration with the laboratory workers associated with its original development, we are now manufacturing this product in quantities sufficient to meet all demands. It is issued in 7 oz. and 16 oz. bottles.

Cream of Colloidal Aluminum Hydroxide (Creamalin) has now been used in several thousand cases of Peptic Ulcer with results justifying a place in its particular therapeutic field.

Creamalin apparently represents a definite advance in ulcer therapy. From clinical reports the advantages may be summarized as follows:

- More prompt alleviation of pain.
- Unusual neutralizing properties—one volume neutralizing as much as twenty-five times its volume of tenth normal HCl by physical fixation (adsorption) as demonstrated by electro-chemical tests.
- Avoids possible danger of alkalosis.
- Tendency to depress HCl output.
- Reduces emptying time of stomach by allaying pylorospasm.
- Ideal demulcent and protective to ulcerated area.
- No toxic effects or contra-indications.
- Economy and simplicity of administration.

#### Clinical Material Available

Gastro-enterologists and clinicians interested in investigating the especial merits of this product can obtain material in any amount they feel necessary to an adequate trial upon application.

Address all communications to Cleveland Chemical Associates, Cleveland, Ohio, stating the number of cases and whether you wish it sent to a clinic or hospital. If convenient, kindly let us know the name of your prescription druggist.

\*Einsel, Adams, and Myers: "Aluminum Hydroxide in the Treatment of Peptic Ulcer." American Journal of Digestive Diseases and Nutrition (September, 1934).

\*From the Soper-Mills Clinic.

Submitted August 5, 1935.

births). Had usual childhood diseases, appendectomy in 1929 and during the past eight years attacks of severe pain in the kidney regions associated with occipital headaches and nausea. Attacks were always relieved within one hour after considerable vomiting. No apparent distress remained after even a severe attack was over.

The family history was negative except that on her paternal side her father and grandfather had suffered similar attacks of lumbar pain, headaches, nausea and vomiting. None was ever for any length of time, incapacitated from the attacks.

The patient, among her acquaintances, was noted for her Madonna-like beauty. However, since 1931, her friends noticed that her beauty was disappearing and that her features were changing markedly. The face was becoming very full and rounded, appeared swollen, features becoming coarse, the skin looked thick and heavy, comedones appearing over the face, and fine and coarse hair appeared on upper lip and chin. This hirsutism was also present on the legs. The weight gradually increased and her blood pressure, according to members of her family, constantly was mounting, a few months prior to her death the systolic was 162.

The patient was seen by me on November 19, 1934, at two P. M. She was conscious and stated that at three A. M. she had an attack of severe pain in both kidney regions. The pain did not radiate but remained constant; has intense desire for urination but passes only a small amount of urine; severe "thumping" at the base of the skull, nausea, vomiting and high fever. Because of the knowledge of the time element in previous attacks, she had delayed seeking medical attention.

The patient appeared to be rapidly approaching complete circulatory collapse. Her entire body was covered with various sized, purplish blotches on a background of bluish cyanosis. The pupils were dilated, temperature 103; respiration 42; pulse 140-soft, regular, thready; heart sounds faint but distinct; lungs negative; blood pressure 120/70; abdomen negative; palpation in both costochondral angles caused an increase in her already agonizing lumbar pain; reflexes normal. One-third grain morphine intravenously was given and it was advised that she be removed to a hospital immediately.

She arrived at the hospital at four-twenty P. M. and was seen in consultation with Dr. Rogers Deakin, urologist. Catheterized urine specimen showed 3+ albumin, specific gravity 1016, many hyaline and a few granular casts, few red blood cells and a few white cells. Urinary findings indicated an acute nephritis. Because of the circulatory collapse further cystoscopy was thought to be contraindicated. External heat was applied, intravenous glucose and

emergency heart stimulants were given. Patient seemed to improve temporarily after repeated injections of 3 c.c. adrenalin chloride given intravenously. The pain was not controlled by large doses of morphine and pantopon. Patient complained bitterly of pain but remained conscious up until a few minutes before her death, which occurred at five-fifteen P. M.

The diagnosis was made at autopsy by Dr. Ralph W. Thompson of St. Louis. The important findings were as follows: The entire body has a peculiar

bluish-red, livid, splotchy appearance. The lower extremities are abnormally hairy. The facial features are somewhat thickened and coarse in appearance. The pancreas is normal in consistency, size and shape, and exhibits no evidence of recent acute inflammation or hemorrhage. The spleen is distinctly abnormal, measuring only approximately 5 cm. by 3 cm. by 2 cm. in dimension. Its external appearance is a dull-slate color, with whitish granulation resembling a coat of "frosting." The pelvic organs are normal. On ex-



*Fall*

*Winter*

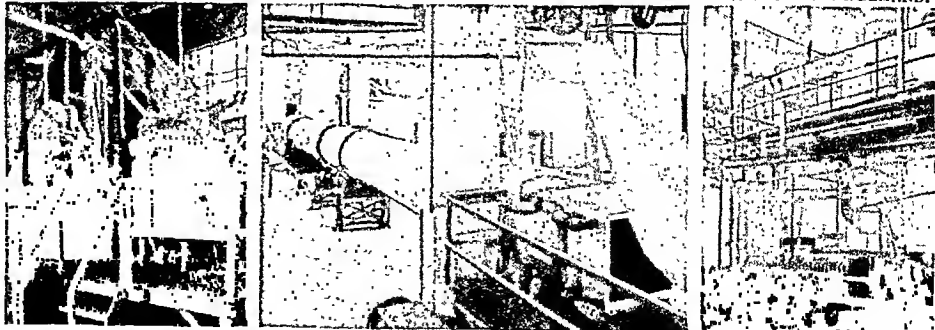
## CAROTENE (PRO-VITAMIN A) IS THE ALL YEAR VITAMIN for ADULTS and CHILDREN



Q Many regard Carotene [Pro-Vitamin A] as a valuable aid in maintaining a healthy condition of the mucous membranes and therefore, believe that it helps to protect against the invasion of pathogenic bacteria. Q Smaco Carotene-in-oil is made from plant sources exclusively. Consequently it has no fishy taste. Small, easy, drop or capsule doses. Q Also offered combined with Vitamin D concentrate.

S.M.A. Corporation ©1935 Cleveland, Ohio

GLIMPSES OF SOME OF OUR EQUIPMENT FOR PRODUCING CAROTENE IN QUANTITIES SUFFICIENT TO MEET THE DEMAND.



amination, the kidneys are found to be somewhat edematous, with congestion of the pyramidal tissue and the renal cortex. There are massive hemorrhages in both right and left suprarenal glands which are approximately two and one-half to four times their normal size. The hemorrhages have distorted the suprarenal cortex so that they have the appearance of hemorrhagic cysts.

*Microscopic examination:* Kidney; glomerular nephritis (moderate degree); pancreas negative; spleen, chronic splenitis with increase of trabeculae and hemorrhage (much pigment from old bleeding); adrenals: marked congestion and massive hemorrhage both old and recent. The recent hemorrhage appeared to be into the medulla, but the cortical cells were extensively loaded with pigment thus indicating an old hemorrhage.

#### TREATMENT

Emergency treatment in cases of massive hemorrhage into the suprarenals, producing practically a complete absence of function of these

glands, if diagnosed, resolves itself into the use of enormous doses (as much as 3 c.c.) of adrenelin chloride and cortical hormone exhibited intravenously, in addition to the usual method of combating circulatory collapse and hemorrhage. The large doses of suprarenal extracts are given in the hope of tiding over the patient during an acute severe hypoadrenal period.

#### COMMENT

This case presents several interesting features; *i.e.*, fatal, massive suprarenal hemorrhage, many minute, former suprarenal hemorrhages (infarcts?), splenic hemorrhages (infarction?), and hyperfunction of the suprarenal cortex.

I feel that we can safely hazard the opinion that the pre-terminal attacks of lumbar pain, occipital headaches, nausea and vomiting were due to the small suprarenal hemorrhages. Nature, in attempting to repair the damage done, overcompensated, and the more or less chronic resulting hyperfunction of the suprarenal cortex occurred as evidenced metabolically by the physical changes in the appearance of the patient such as today we recognize as a part of the suprarenals' cortical syndrome (hirsutism, changes in nutrition and physical appearance; progressive arterial hypertension).

The macroscopic and microscopic findings in the spleen add another interesting angle to the picture. The part played by that organ is not understood at the present time.

In considering the differential diagnosis, one must consider with any confused picture of lumbar pain which is associated with headaches, nausea and vomiting, always the possibility of minute suprarenal hemorrhages.

#### REFERENCES

1. (a) Gunson, E. B.: *Proc. Roy. Soc. Med.*, viii, 52, 1914-15.  
 (b) Endie, J.: *Practitioner*, xcix, 183, 1917.  
 (c) Lusk and Brumbaugh: *J. A. M. A.*, lxxii, 1062, 1919.  
 (d) Goodhart and Still: *Diseases of Children*, p. 517, 1921.  
 (e) Severn, A. G. M.: *Lancet*, i, 647, 1923.  
 (f) Kempf, H.: *Viertel-Jahrschrift für gerichtliche Medizin*, lvi, 71, 1918.  
 (g) Rabinowitz, M. A.: *Am. Jour. Med. Sci.*, clxvi, 513, 1923.  
 (h) Kessell, J. S.: *Med. Jour. of Australia*, ii, 456, 1925.  
 (i) Henderson and Pettigrew: *Brit. Med. Jour.*, i, 14, 1932.  
 (j) Pearl, F., and Brunn, H.: *S. G. and O.*, 47:393, October, 1928.
2. Rabinowitz, M. A.: *Am. Jour. Med. Sci.*, clxvi, 513, 1923.

## IN LINE WITH

# Preventive Practice

CONSTIPATION due to insufficient "bulk" is often a result of the average American meal. Unless checked, it may well lead to serious trouble.

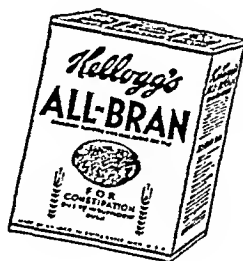
However, the continued use of cathartics is often harmful, because of the tendency of these drugs to form dangerous habits. It's much better if people can obtain the needed "bulk" in the foods they eat.

Kellogg's ALL-BRAN is a convenient source of "bulk" to aid regular habits. This "bulk" does not lose its effectiveness when used regularly. ALL-BRAN also supplies vitamin B and iron, an important element of the blood.

The "bulk" in this natural, laxative food is mild in action. It does not break down in the body as much as the "bulk" found in fruits and vegetables. So it is often more effective.

ALL-BRAN may be used with perfect safety by most people. A few individuals have highly sensitive intestines. In these special cases, any form of "bulk" is, of course, inadvisable.

This delicious cereal may be served with milk or cream or used in cooked dishes. Sold by all grocers in the red-and-green package. Made by Kellogg in Battle Creek.



## Kellogg's ALL-BRAN



## A B S T R A C T S

I. S. WECHSLER.

*Abdominal Pain as a Symptom of Disease of the Brain. J. A. M. A., 105:9, August 31, 1935.*

Abstracts of 14 cases are reported by this observer of brain lesions in which abdominal pain was a prominent symptom. He states that it probably occurs more often than appears from a casual observation and that special attention will bring to light a greater number of cases. His paper deals with expanding lesions which are of such great importance to the neurologist and neurosurgeon. Most of the evidence presented points to the cortex and possibly to the frontal, more particularly the premotor area as the source of neurogenic abdominal pains and indicates that the cortex contains visceral autonomic representation. But there is also evidence to show that the hypothalamus and possibly the vagus region may be responsible for the abdominal pains, and that if the cortex is the source of the pain it is mediated by way of the lower levels or centers. The symptom, therefore, cannot be said to have localizing value, though it may point to the frontal part of the brain.

T. H. Morrison, Baltimore.

ROSEDALE, RAYMOND S., M.D.

*"Jejunal Diverticulosis." S., G., and O., 60:223-228, August, 1935.*

Autopsy findings are presented in three cases of jejunal diverticulosis—in one, there was an associated multiple diverticulosis of the colon and in another, an associated parasitic infestation of the jejunum. While gastro-intestinal symptoms are usually absent in patients with jejunal diverticulosis when present they resemble in general those of chronic duodenal stasis. Various reports have described pain 1 to 3 hours after eating, nausea, vomiting, distension, barbarygmus relieved by change in position, melena, constipation, a fecal taste associated with vomiting, and a syndrome suggestive of low grade intestinal obstruction.

Two very excellent photographs of contrast X-ray study are included in the article.

J. Duffy Hancock, Louisville.

OPPER, LINCOLN.

*Congenital Megacolon. Am. Jour. Path., Vol. XI, No. 2, p. 365, March, 1935.*

The report of a case of *megacolon congenitum* (Hirschsprung's disease) is given which presents two points of interest; first, the nature of the death of the patient, which was due to com-

pression of the heart and lungs by the distension of the colon; and second, both the absence of any mechanical obstruction about the rectum which might have been considered etiological in relation to the disease and the absence of any apparent change in the cells of

Auerbach's plexus within the wall. In this case the bladder did not take part in the dilating process, as has been described in some instances.

The author reviews very briefly the theories of causation. It is evident that his case fits into a neurogenic etiology

## SOOTHING • ANTACID GENTLY LAXATIVE . . . .

• • • • Gastric and intestinal disturbances usually go hand in hand. In the presence of a gastric hyperacidity, there is often a sluggish bowel.

A rational measure in the treatment of constipation or gastric hyperacidity is provided in



(An emulsion of Milk of Magnesia and Pure Mineral Oil)

• • • • Combines the gentle laxative and effective neutralizing properties of milk of magnesia with the lubricating action of mineral oil, in a fine, palatable emulsion.

SAMPLE TO PHYSICIANS, ON REQUEST.



## The Chas. H. Phillips Chemical Co.

170 Varick Street

New York

N. Y.

better than into other groups. The mechanism of death was apparently unusual, for the cause of death in Hirschsprung's disease as recorded in the literature is usually that of cachexia or perforation of the intestine in relation to an ulcerated colon and the related colitis. The patient died suddenly of acute heart failure at a time when he had been in comparatively good health.

N. W. Jones, Portland.

SEELY, HALL, M.D., AND ZOLLINGER, ROBT., M.D., F.A.C.S.

"Fundusectomy in the Treatment of Peptic Ulcer—An Experimental Study." *S., G., and O.*, 61:155-161, August, 1935.

The surgical treatment of peptic ulcers has been rather satisfactory in the management of perforation, hemorrhage, and obstruction but much less so in permanently lowering gastric acidity. This latter is true even when an attempt is made to permit easy regurgitation of the alkaline duodenal secretion

and at the same time to eliminate the ulcer bearing area. An ingenious study of the gastric mucosa of a dog showed that while acid secreting cells were present in practically all locations, they were much more numerous in the fundus as has been demonstrated before. These cells were also found more abundant in the greater curvature because of the great reduplication of the mucous membrane by the rugae. In a series of four dogs, the acidity was determined by various analyses and fundusectomy was done, leaving only a tubular passage along the lesser curvature. The immediate post-operative drop in free and total acidity began to ascend after 3 months and at 8 months had reached the preoperative levels. The dogs were then sacrificed and grossly the stomachs showed an approximate return to normal size and shape. Microscopic examination showed a general distribution of acid reacting cells thruout. The conclusion offered is that since the gastric acidity cannot be permanently lowered by excision of the acid bearing portion of the stomach fundusectomy has little to offer as a therapeutic measure in the control of peptic ulcer.

J. Duffy Hancock, Louisville.

PASS, I. J.

*Infarction of the Liver.* *Am. Jour. Path.* XI, 64, p. 503, May, 1935.

The rarity of infarction of the liver prompts the author to discuss the literature on the subject and report 2 additional cases with autopsy and histological finding. 3500 autopsies were held at Johns Hopkins Hospital without encountering a single case. There were 2 cases noted in 23,000 autopsies at the University of Minnesota. Chiari saw but 2 cases in 21 years experience. It has been assumed that the simultaneous occlusion of both the hepatic artery and the portal vein was necessary to produce true infarction of the liver.

The author's first case was a white male, aged 27 years, who complained of pain in the abdomen following a trauma suffered a month previously. He lived 48 days after onset. The liver weighed 2000 grams. The surface was bluish red and showed numerous irregularly shaped depressed areas. Cut section showed infarcts of different sizes and shapes. The vessel supplying one large red infarct was closed by a small red plug. Most of the infarcts were white; some contained a brownish fluid. Microscopic examination of the kidneys, liver, heart, and spleen revealed a marked involvement of the small arteries. Thrombi were present in many of the larger arteries of the kidneys, spleen and liver. There was complete necrosis of all the tissue elements in the infarcted areas of the liver. The anatomical diagnosis was periarteritis nodosa; multiple infarcts of kidney, spleen, liver and stomach wall; hemor-

## The World's Most Famous Natural Alkaline Water

PRESCRIBED BY  
PHYSICIANS THE  
WORLD OVER

VICHY CÉLESTINS, the most famous of natural alkaline mineral waters, is indicated in stomach and liver affections and digestive disorders in general; in gout, arthritis associated with uric acidemia, uricemia, and nephrolithiasis of uric acid origin. During convalescence, it eases and expedites the journey back to health. Vichy Célestins is obtainable everywhere.

BOTTLED ONLY AT THE  
SPRING IN VICHY, FRANCE



# VICHY CÉLESTINS

Write for booklet on Therapeutic Value of Vichy with Medical Bibliography.  
AMERICAN AGENCY OF FRENCH VICHY, INC., 198 Kent Ave., Brooklyn, N. Y.

rhage from left kidney; hemorrhage from ulcer of stomach.

The second case was a white male, 24 years of age, who had not recovered from an "influenzal attack" four months previous. He suffered abdominal pains and died of inanition. The liver weighed 1500 grams; was olive green in color and the surface was nodular. These areas on cut section were yellowish, and proved to be infarcts. The hepatic artery was closed by the tumor mass originating in the stomach. The anatomical diagnosis was carcinoma of the pyloric end of the stomach with metastases to the pancreas, periaortic lymph nodes and lesser omentum; obstruction of the common bile duct and hepatic artery; ascites; multiple infarcts of the liver and spleen.

N. W. Jones, Portland.

CANTAROW, A., AND STEWART, H. L.

*Alteration in Serum Bilirubin and Bromsulphalein Retention in Relation to Morphological Changes in the Liver and Bile Passages in Cats with Total Biliary Stasis. Amer. Jour. Path., XI, 64, p. 561, May, 1935.*

An attempt is reported to correlate changes in hepatic function with the morphological changes in the liver at

varying intervals during the bile stasis in experimental animals.

Determinations of the serum bilirubin concentration and degree of bromsulphalein retention were made almost every 24 hours in 29 cats with complete ligation of the common bile ducts over periods of time as long as 16 days. Sections of the livers were made simultaneously. The sections showed early dilatation of the bile ducts, proliferation of the smaller ducts, and, particularly after the 10th day, a marked proliferation of the mucosa of the larger ducts. Regressive changes were noted in the inner portion of the nodule, immediately beneath the capsule, sporadically throughout the parenchyma and about the larger bile ducts. Necrotic cells were constantly being replaced by regenerated hepatic cells until a terminal stage of stasis was reached. Local areas of necrosis began by the end of 5 hours, were most marked between 24 and 48 hours, and were absent after the 13th day. Hyaline necrosis of the hepatic cells within the lobules began within 24 hours and they were constantly replaced by newly regenerated cells. After the 5th day a concentric avascular fibrosis began. The branches of the hepatic and portal veins were often occluded by hyaline or fibrinous thrombi. Evidences of regeneration characterized by bud-

ding and fission of the nuclei were formed within 8 hours and this gave way to mitotic division of the hepatic cells by the end of 48 hours.

From the chemical studies conducted daily on the animals the authors found that a marked degree of individual variation in serum bilirubin concentration existed. The highest incidence of concentration occurred early in the second week of stasis, and declined thereafter. The time of the initial fall seemed to coincide with the disappearance of mitotic figures in the hepatic cells. There was no demonstrable correlation between the morphological changes and the concentration of serum bilirubin at any given time during the period of total bile stasis. The degree of bromsulphalein retention varied greatly and was not consistently related to the duration of stasis or to the concentration of serum bilirubin. There was no apparent correlation between the degree of dye retention and the morphological changes present in the liver or bile ducts. And, finally, the variation in dye retention might be dependent upon several variable factors, namely, destruction, storage, or extra-hepatic elimination of the dye.

N. W. Jones, Portland.

## ● TILDEN Has Kept Faith With Physicians ●

# ELIXIR MALTOPEPSINE (TILDEN)

*For prescription in gastric and intestinal  
upsets of starch and protein digestion*

- ELIXIR MALTOPEPSINE (Tilden) is an elegantly flavored preparation, prescribed for alleviating symptoms, and as a vehicle for administering other therapeutic ingredients without untoward effects.
- It contains essentially Dioscorein, Lactic Acid, Diastase and Pepsin with other ingredients, combined in a manner exclusive with Tilden.
- The prescription specialties of The Tilden Company have been used under the direction of physicians for nearly a century, and have never been advertised to the laity.

Medical literature will be supplied on request to physicians only.

*Inquire for the new gluconate tablet adjuvant to Maltopepsine.*

# THE TILDEN COMPANY

*The Oldest Pharmaceutical House in America*

New Lebanon, N. Y.

AJDD 10-35

St. Louis Mo.

B. C. SMITH, M.D.

*Primary Perforated Jejunal Ulcer.*  
*Annals of Surgery, Vol. 101, No. 5,*  
*May, 1935.*

The author gives a detailed case history of a patient under his observation with a primary perforated jejunal ulcer—this being the 26th case of this kind reported in the literature.

This condition is a very rare clinical entity having been found in only 17 instances among 17,518 autopsies at Bellevue Hospital, New York City. Dr. McCarty, Department of Pathology at the Mayo Clinic, does not know of a case of primary jejunal ulcer with perforation during the 25 years he has been at the Mayo Clinic.

The etiology remains unknown and the author has no adequate explanation to add.

From a review of the 25 cases reported in the literature and from the history of the case he reports, which was operated upon with suture of the ulcer and recovery, the author states that the most frequent symptoms noted are pain, localized above and to the left of the umbilicus; usually made worse by eating; non radiating; appearing at no appointed time as regards meals and of a dull boring character. Some

patients would be free of pain for intervals of 2 or 3 months at a time. Nausea occurred occasionally but there were few cases with vomiting. The stools in all suspected cases should be searched for occult blood.

Pathologically the ulcers have shown no exact pathological picture except of inflammation and ulceration. The size varied from 2 mm. as in the authors case, to 2 cm. These ulcers in the majority of cases were found on the antimesenteric border of the jejunum—the chronic ones having the tendency to cicatrize and occlude the gut.

The author includes in his article brief case reports of each of the other 25 cases of primary perforated jejunal ulcer found in the literature.

The author suggests the term, "Primary Jejunal Ulcer" to mean an ulceration of the jejunum where there had not been a preceding operative procedure on either the stomach, duodenum or jejunum, and the term "Secondary Jejunal Ulcer" to denote an ulcer in the jejunum following some operative procedure on the stomach, duodenum, or jejunum.

Charles T. Sturgeon, Los Angeles.

## RECORD FORMS FOR THE ASKING

It has been our privilege and pleasure to work with the medical profession in compiling clinical record forms that have furnished the basis of findings in the successful treatment of diseases of the GASTRO-INTESTINAL TRACT.

To assist you in keeping the proper clinical records we have created a clinical record form, double letterhead size, folding to 8½ x 11. The first page is a case history, the second page physical examination, the third page laboratory report and the fourth page is progress records. These forms are furnished to the medical profession WITHOUT CHARGE . . . they are yours for the asking.

## TAUROCOL

(TOROCOL)

### Bile Salts Tablets

Recent clinical tests show that Taurocol "stepped up" the flow of bile as much as 150%.

TAUROCOL is a combination of bile salts, extracts of cascara sagrada, phenolphthalein and aromatics and is an agent recognized by the medical profession and widely prescribed for about a quarter of a century.

The Paul Plessner Co.

Detroit - - - Michigan

J. D. 10-35

## Viable Bacteria Reduced To Zero (Or Near Zero)

In 15 series of samples of the defecate from a number of human subjects. The subjects were not injured by the medication, as determined by thorough clinical and laboratory examinations immediately after cessation of medication and for a number of months subsequent thereto.

The medications employed were two saponaceous glycerites of Alpha Naphthol designated:

## ALPHA NAPH CO AND JELLY OF ALPHA NAPH CO

The Alpha Naph Co was taken in water and orange juice. The "Jelly" was administered in enteric coated capsules opening in the intestinal tract.

A resume of the reports, and adequate supplies for clinical test, will be gladly sent to any physician interested, with our compliments.

CAREL LABORATORIES  
REDONDO BEACH - - - CALIFORNIA

# SECTION I—*Clinical Medicine: Diseases of Digestion*

## GALL STONES

By

A. J. DELARIO, M.D.\*  
PATERSON, NEW JERSEY

IN a study of 14,000 gall bladders, Mentzer (21) found 57% of the surgical specimens, and 20% of the autopsy specimens to contain stones. If cholesterosis were to be included, then gall bladder precipitation was found in 69.87% of the surgical specimens, and in 37% of the necropsies. This study shows that precipitation of bile constituents is very frequent, and it seems therefore that a discussion of this subject would be of value.

### CHEMICAL COMPOSITION OF GALL STONES

Gall stones may consist chemically of pure cholesterol, or of 20 to 90% of cholesterol, in conjunction with calcium carbonate, calcium phosphate, and especially calcium bilirubinate. Cholesterol stones are found mainly in humans; they may be round or faceted.

Some stones are made up only of bilirubin, or its calcium salt. These are small, black or greenish. This is the most common type of stone in oxen and pigs, where they may reach the size of a walnut.

Occasionally biliverdin and bilifuchsin will form a stone which likewise will be small and green.

In about 3% of cases calcium carbonate or phosphate may be the sole constituent of a stone. These stones are hard, and show very well by X-ray. About as often as it forms stones, calcium carbonate precipitates in the form of a mud or milk. Calcium stones are very frequent in cattle and pigs.

Iron and copper are found in minute quantities in stones. Manganese and zinc have been found occasionally, and in some stones have been found cell debris, bacteria, mucin, etc. (15).

Depending upon the amount of cholesterol present, stones are either heavier or lighter than water. Pure or nearly pure cholesterol stones float, those with a great deal of calcium will sink.

Cholesterol is the main constituent of human gall stones. Most investigators have failed to find it in the stones of other animals. Mentzer, however, found it in the gall stones of swill-fed hogs. Those fed on grain did not have it. He found three cholesterol gall stones in 252 swill-fed hogs, and he found four bili-

rubin calcium stones in 712 grain-fed hogs. Only 0.72% of 964 pigs' gall bladders had stones. In 400 sheep, 1.75% of which had stones, one cholesterol stone was found. In the other six, bilirubin-calcium stones were found (22).

Gauss and Davis found cholesterol-rich stones in 1% of cattle (13). Whales have large biliary concretions known as ambergris, sometimes weighing as much as 100 pounds, which are claimed to be cholesterol stones (10).

Cholesterol is a monatomic alcohol ( $C_{27}H_{45}OH$ , or  $C_{27}H_{45}OH$ ) (19), and is a solid at temperatures as high as 148.4 degrees C (body temperature is 37 degrees). It is insoluble in water. It is soluble in bile salt solutions. When cholesterol is precipitated slowly, beautiful compact crystals are formed, usually flat, with a corner broken off one end; the angles of the sides are 76° 30' and 87° 31'. A solution of these crystals in chloroform or ether is levorotatory. A 2% solution turns the plane of polarized light 31° 12'.

When cholesterol is allowed to precipitate rapidly it forms a feathery network of almost amorphous material, with fine perfect crystals at the end of each network.

It is interesting, especially in the study of the etiology of cholesterosis to note that cholesterol is excreted by the whole gastro-intestinal tract, mainly by the large bowel. It is present in biliary and pancreatic excretions, and the cholesterol found in the mucous membrane of the gall bladder in cholesterosis is probably an expression, therefore, of excretion rather than absorption.

Bilirubin ( $C_{33}H_{36}N_4O_6$ ) (31) and its salts can be of reddish yellow or brown crystals, or amorphous material. The crystals are relatively insoluble in water. Bilirubin crystallizes in long needles from chloroform solution. Solutions of bilirubinate easily precipitate with lime salts, especially in dilute alkalis.

Salts of biliverdin ( $C_{33}H_{38}N_4O_6$ ) (18) are usually amorphous and also insoluble in water.

Salts of calcium, such as carbonates and phosphates, are insoluble in water.

As one can see, the biliary constituents that form stones are insoluble in water. Cholesterol is held in solution when the bile salts are present to the extent of 13 times the amount of cholesterol present. This is the critical level of cholesterol precipitation (1).

\*Assistant in Gastroenterology and Associate in X-ray, St. Joseph's Hospital, Paterson, N. J.

Submitted July 22, 1935.

Thanks are due to Dr. Harry Golding, Head of the Roentgen Ray Department, St. Joseph's Hospital, for his kindness in permitting the use of many of the X-rays presented in this paper, and to Dr. Kim, Pathologist, of St. Joseph's Hospital, for his aid in obtaining certain gall bladders and stones illustrated here.



Fig. 1. Group of pectolite crystals showing one method of crystallization in nature, with crystals radiating from a given point or center.

Bilirubin stays in solution up to a certain point, and according to Elton (9) precipitation occurs when its concentration by the gall bladder is 50.9 in dogs, 40.4 in cats, and in humans even much higher.

Calcium carbonate and phosphates are extremely insoluble, and have a great tendency to be present wherever cholesterol is found, as is evident in atheromas of the blood vessels and calcification in the lung, etc.

Calcium is probably normally excreted by the gall bladder, and its excretion is increased in the presence of infection and stasis (23). One gathers from Phemister's article (23) on calcium carbonate stones, that calcium carbonate may be excreted as such by the gall bladder in some cases or that calcium exists in a soluble ionic form and is rendered insoluble by its union with carbon dioxide ions when pH or the number of carbon dioxide ions reach a high level in the gall bladder under pathological conditions. And this may occur even though the amount of soluble calcium ions found in the gall bladder is higher or lower than normal (24).

The precipitation of biliary elements, like crystallization in nature, takes place in the main by two methods:

1. Crystallization may occur about a given point or center, just as is shown in the crystallization of pectolite (Fig. 1). Additional layers may be added on to it later.

2. Crystallization may take place from the outside first, crystals being deposited on the inner shell from the salts present in the liquid captured at the center, as is shown in the geode of quartz (Fig. 2). The crystals at the outside being very small, and those toward the center being large, due to the slower rate of crystallization.

The stones that form from a given center are round when they are formed in the fundus of the gall bladder, and if they occupy the entire fundus they become oval, just as the gall bladder fundus is oval.

If two such stones are formed in the fundus of the gall bladder, then, where the two stones meet, crystallization continues in a fashion that makes the stone flat at this point. Crystallization at the flat surfaces is cramped. The crystals are smaller. Peculiar de-

formed, crowded or flattened "liesegang," ring phenomena, are seen at this area of contact, that show the cramming of crystallization.

As the various centers of crystallization in the gall bladder fundus increase, then of course the number of flat or irregular surfaces increase to a point at which the stones are called "facetted."

In this type of stone, in which crystallization proceeds from the center, crystallization is usually very slow. The crystals can be seen, large and shiny, radiating from a given center (Figs. 3 and 4); as crystallization occurs the calcium bilirubinate is pushed outward, and but very little of it is caught between the plates of cholesterol. If crystallization is a little faster, then the plates are smaller, and more pigment is caught between them (Fig. 5). As the rate of crystallization increases in this type of stone, the centers of crystallization usually increase. The cholesterol crystals are very fine, needle-like, and more pigment is found between crystals, and in fact, quite a clump of it may be found at the very center of the stone (Fig. 6).

When the rate of crystallization is very rapid in a large stone, the stone will have a moth-caten appearance. The crystals will be small and needle-like, and radiate not from a given point, but from a large mass of pigment which may even contain a cavity (Fig. 7).

We have round, or nearly round, stones and facetted stones in which crystallization started from the outside first, and proceeded inward (Fig. 8). In these stones there is usually a hollow center, as one examines them some time after they have been removed from the body. This is due to evaporation of water which normally exists at the center. If one cracks one of these stones immediately after removal he will find the shell thin, and the center moist, or filled with fluid. In this type of stone the crystallization has been much more rapid, as one can tell by the size of the crystals as seen under the microscope when compared with the size of the crystals removed from the stone in which crystallization took place from the inside first (Fig. 9). The size of the crystals from the facetted stones is similar to the size of the crystals when cholesterol

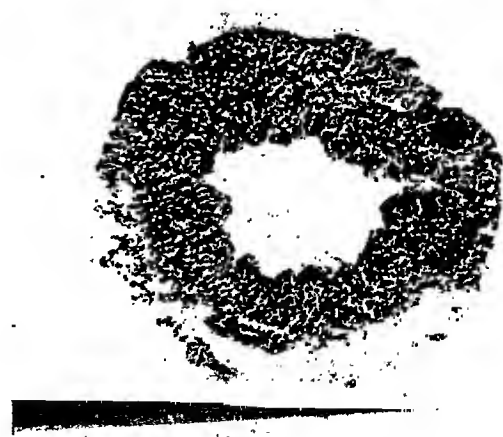


Fig. 2. A geode of quartz showing another method of crystallization in nature in which crystallization occurred in the periphery first and proceeded inward, crystals on the outside being small and those toward the center being large, due to the slower rate of crystallization.





Fig. 3. Large cholesterol stone in which crystallization proceeded from a given center. Crystals are large, flat, and shiny, with very little pigment caught between crystals. These facts point to a slow rate of crystallization.

is allowed to precipitate rapidly from a solution of acetone (Fig. 10).

The cholesterol stone has no crystalline form at all when seen grossly, but is fatty and compact in nature, and at the center bile pigment is found in large amounts. The cholesterol seems to be in compact or flat layers.

In this type of faceted stone in which crystallization occurred from the outside first and proceeded inwardly, it seems that it is the cholesterol which precipitates first in definite zones throughout the gall bladder, the facets being determined by these different zones which cause stress upon one another. The crystallization is very rapid, all the zones crystallize at the same time, and due to the nature and composition of the bile at that time, each stone would be more or less of the same form, size, shape, color, and each stone would have the same identical internal pattern. The size of the stone, the amount of fluid caught at the center, the "liesegang" or ring phenomenon, all depend upon the speed of crystallization.

Figure 11 shows a stone which has the characteristics found when crystallization radiates from the



Fig. 4. A photomicrograph of crystals removed from the center of the stone in Fig. 3. Shows large crystals of cholesterol.

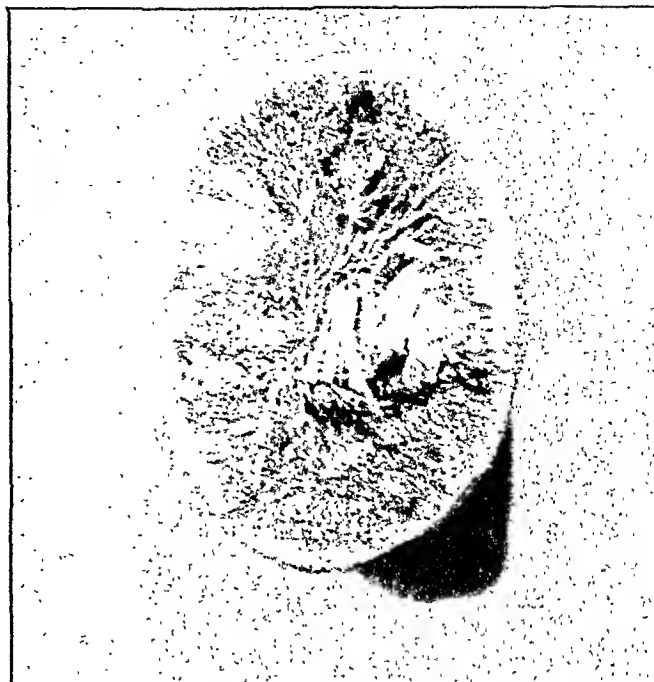


Fig. 5. Cholesterol stone in which crystallization proceeded from a given center at a slightly faster rate than in the stone seen in Fig. 3. The cholesterol crystals are smaller; more pigment is caught between crystals.

center, and also a flat band typical of the rapid crystallization found in a faceted stone in which crystallization started from the periphery first. This stone therefore signifies a rate of precipitation midway between that found when crystallization starts from the center and that found when crystallization starts from the outside.

I have mentioned the speed of crystallization many times, and in this connection the chart (Chart I) taken from the book "The Natural History of Crystals" by A. E. Tutton (29) is interesting. Here one can see

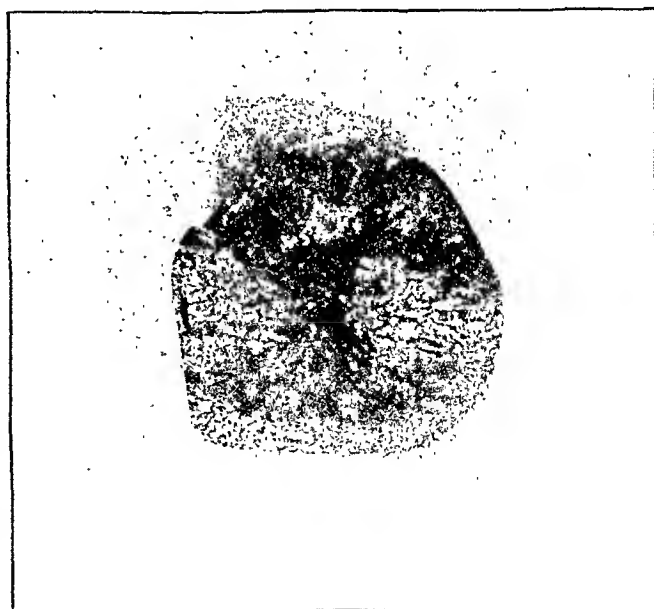


Fig. 6. Cholesterol stone in which crystallization proceeded at a still faster rate than in the stone in Fig. 5. The cholesterol crystals are smaller, more needle-like, and more pigment is found between crystals.



Fig. 7. Cholesterol stone in which the crystals radiate from a cavity containing pigment or fluid. Here crystallization has been faster than in any of the previous stones.



Fig. 8. Facetted type of stone; shows crystallization starting from the outside and proceeding inward. They have a hollow center, grossly appear fatty and compact in nature, and in flat layers. The cholesterol crystals are very small, indicating very rapid crystallization.



Fig. 9. Photomicrograph of scrapings of stone seen in Fig. 8, showing the small crystals of cholesterol at "A", crystals similar to those found in Fig. 10.

that there is a definite relationship between concentration and temperature and the rate of precipitation and that when the concentration is very large, precipitation will take place very rapidly. This must occur in faceted stones, especially those with a hollow center, because here the size of the crystals is very small and indefinite.

How long it takes the faceted stone to precipitate in the body has yet to be proved clinically. Can it take place overnight? I believe it can.

Harries (16) found that gall stones probably can occur within three months. A patient, from whom he removed two stones, one-half inch in diameter, had one year later, over a dozen stones, one-eighth to one-fourth inch in diameter. However, the patient gave symptoms of stones three months after the first operation.

I know of a case which, after cholecystectomy, continued to pass stones through a drainage wound for weeks, although at the time of operation no stone was

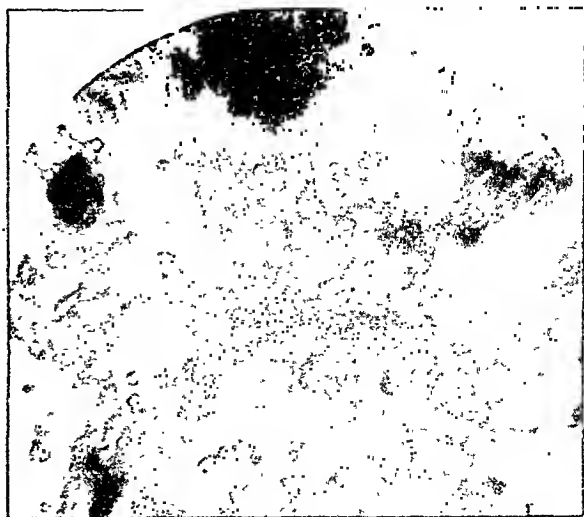


Fig. 10. Small crystals of cholesterol formed when cholesterol is allowed to precipitate rapidly from an acetone solution. Note close similarity to crystals in Fig. 9.



Fig. 11. Facetted stone in which the rate of precipitation is nearly midway between that found in a cholesterol stone in which crystallization proceeded from a given center and one in which crystallization proceeded from the outside first. Notice the flat band at the top of the stone characteristic of facetted stones.

left in the biliary tree, as could be seen by exploration of the common duct.

One can also see from Chart 1 that temperature plays an important part in crystallization. Not only does temperature allow more cholesterol to go into solution when patients are afflicted with temperatures of long duration, but whatever causes a rise in temperature usually causes more cholesterol, bilirubin, etc., to be destroyed. When the patient's temperature is restored to normal, the cholesterol which was held in solution due to higher temperature, tends to precipitate.

If one examines these facetted stones closely by cutting into them, no matter how many stones are present in a single case, the internal form is always the same.

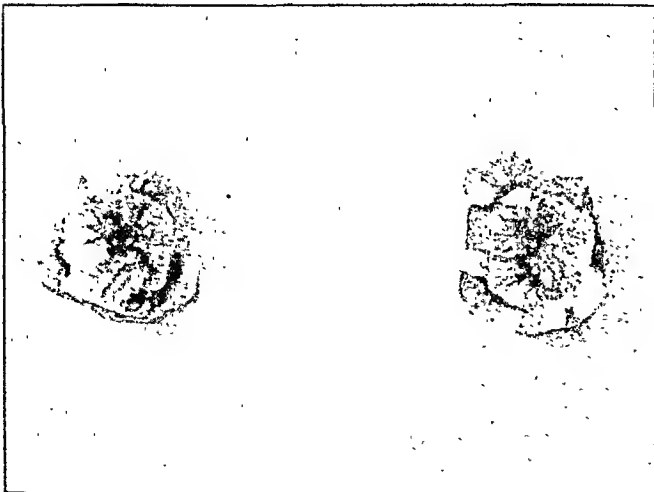


Fig. 12. Cholesterol precipitation upon a previously formed stone. The outer layer of crystals can be completely removed. Air spaces and potential spaces exist between the two areas of crystallization.

In order for so many stones of this identical internal structure to have been formed, they would all have had to be formed at one time, because the chemical composition of bile is constantly changing and the chances are that the same chemical composition and the same factors which have existed at one time in the bile may never occur again, except in a probable ratio of one to millions. If this is so, it would mean that all of the stones would have to be formed at one time.

Occasionally two different types of facetted stone may exist in the same patient, which means that gall stone formation took place probably at two different times, and often facetted stones may exist in which a second precipitation occurred upon a previous stone (Fig. 12). Occasionally round stones signifying a slow rate of crystallization, and facetted stones signifying a rapid rate of crystallization, may be found in the same patient, but both types were probably not formed at the same time. Facetted stones are characteristic of the patient from whom they come. The outside form of gall stones from ten different patients

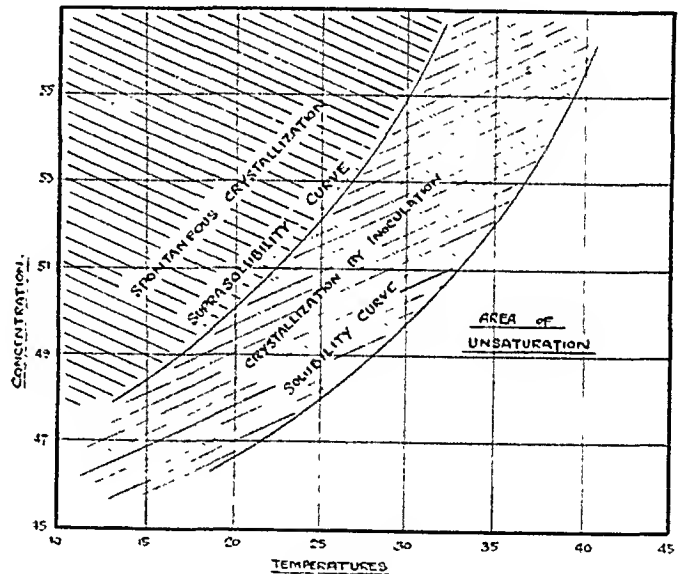


Chart 1. Diagram illustrating the conditions for crystallization from solution or liquid states. Taken from: Natural History of Crystals. (Kegan Paul, Trench Bruden & Co., Ltd., London, 1924). A. E. Tutton, page 44.

may be the same; however, the internal form of the stones of these different patients is different. In fact one can pick all of the stones that come from each different patient merely by opening the stone and examining it.

#### "LIESEGGANG" RINGS

"Liesegang" phenomena can occur in stones of both types of crystallization, internal, and external, in round or facetted stones. Most people believe that the rings signify additional layers deposited on previously formed stones, but Sweet (25) believes otherwise. He believes that the preliminary step must be a colloidal formation, partly a jelly, as often cholesterol can be, and that the black rings are due to rhythmic precipitation of calcium bilirubinate throughout a colloidal cholesterol mass. That this is probably true is clearly shown in the facetted stones, where the precipitation at the corners has been duplicated by him artificially by

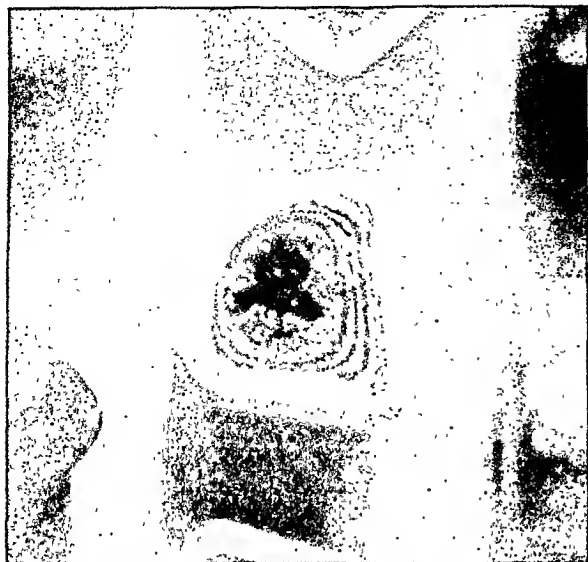


Fig. 13. Showing in a faceted stone the "liesegang" rings formed by the rhythmic precipitation of calcium bilirubinate, the source of which was the bile entrapped at the center of the stone.

means of silver nitrate and potassium bichromate jelly. Usually the source of the calcium bilirubinate is in the bile around the cholesterol mass. Occasionally it is the entrapped bile at the center of the faceted stone (Fig. 13).

Up to this point cholesterol stones only have been discussed. Now calcium and pigmented stones will be briefly dealt with. Calcium salts may exist in great amounts in cholesterol stones either in the "liesegang" rings, or when caught between cholesterol crystals, or when caught along with biliary pigments at the center of the hollow stones.

Sometimes calcium bilirubinate is laid in layers around a previously formed cholesterol stone. How-

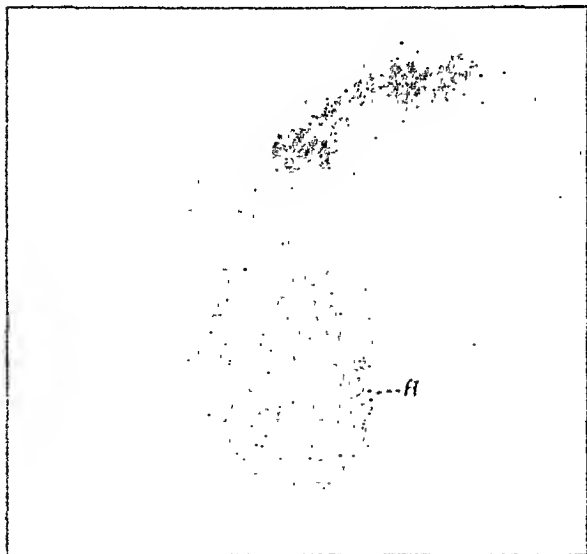


Fig. 14. Calcium carbonate stones found in the cystic duct, and calcium mud found in the fundus of the gall bladder at "A".

ever, calcium may form pure calcium carbonate stones or those in which calcium carbonate is associated with calcium phosphate in smaller amounts. These stones are hard, irregular, and spikey, although the general form tends to be round (Fig. 14). Calcium carbonate may be present as a milky mud just as often as it is present as stone (Fig 15). In fact the bile in the whole gall bladder may have this milky-mud appearance. The X-rays show this mud as a dense shadow. The gall bladder does not visualize with dye, although the cystic duct is not actually blocked, for bile, or this mud, can be squeezed from it.

Biliary pigment may be associated with cholesterol stones in about the same fashion as are calcium salts. In fact they may both appear together as calcium bilirubinate.

Bilirubin, or calcium bilirubinate, may form round or irregular stones which are black, or silvery black, soft, or hard, depending upon the amount of calcium

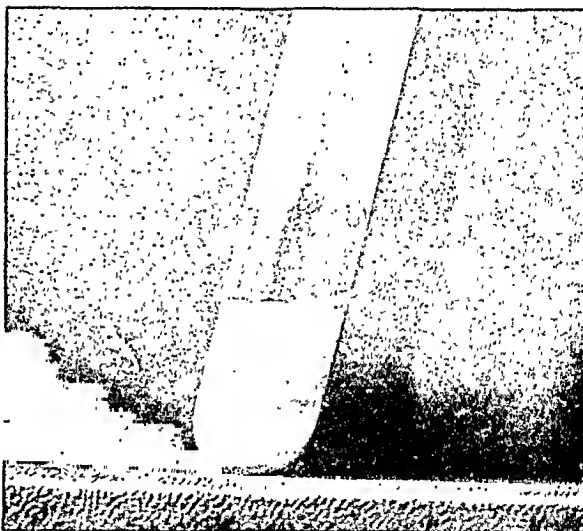


Fig. 15. Test tube with calcium carbonate mud taken from gall bladder.

present (Fig. 16). In some cases it appears that these pigmented stones are merely concentrated masses of pigment due to ante—or even—post-mortem precipitation.

Up to this point it has been shown that the rate of crystallization determines the shape and size of the stone, whether it will be round or faceted, whether crystallization will proceed from the center, or the periphery of the stone and whether or not there will be entrapped bile at the center. It has also been seen that the rate of crystallization depends upon the temperature and concentration of biliary constituents. The factors which cause abnormal concentration of these constituents of bile are given in Table 1.

If these factors are kept in mind in treating patients the conditions essential for gall stone precipitation may be avoided. For instance, if a patient is being treated for a condition in which temperature is of long duration, and the patient is refusing food, he should probably be given bile salts three times a day. Bile salts keep the upper biliary tree free from stasis. They



Fig. 16. Two types of pigmented stone.

Working on lower animals, especially the dog, in 1930, in a paper on the paths of absorption and excretion of sodium tetraiodophenolphthalein (6), I showed, that as far as this dye was concerned, it could be absorbed from the gall bladder wall. In 1931 in a paper on the interpretation of gall bladder roentgenograms (7), I again was of the opinion that all experimental work and data up to that time pointed to the fact that the gall bladder could absorb its dye.

But the Roentgenograms in Figs. 17, 18, 19, present to my mind conclusive evidence that the gall bladder may also empty its contents by contraction. One can see in these roentgenograms that as the gall bladder

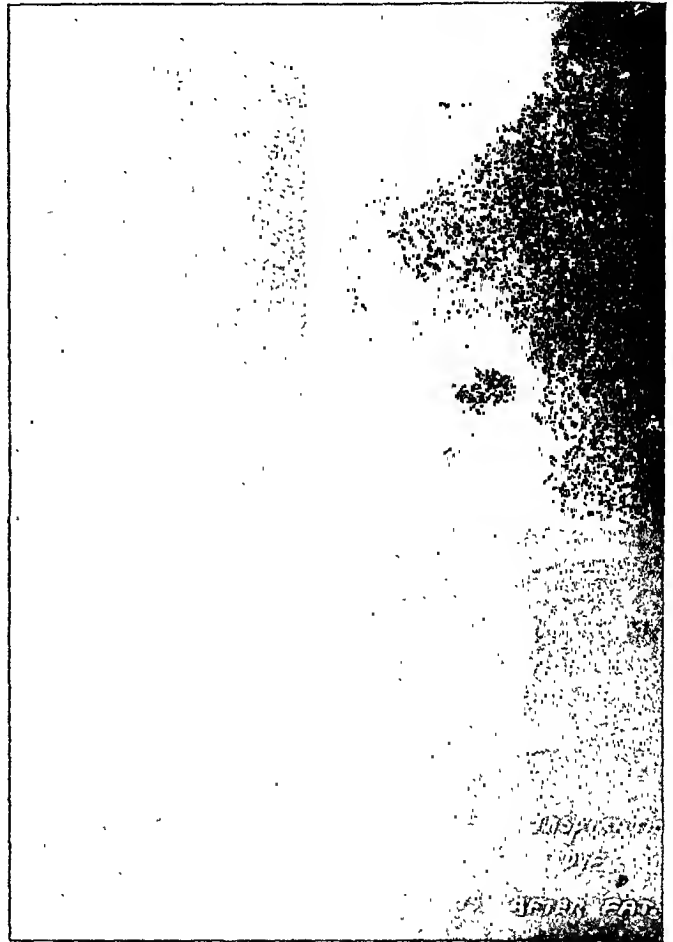


Fig. 18. Fifteen minutes after a fat meal the gall bladder shadow is getting smaller, and the dye in the duodenum is increasing in amount, having the density of bone at "A".

shadow diminishes after a fat meal, the shadow in the duodenum gets larger, and also in this case much denser. This can be explained by the fact that when the bile-containing dye comes into contact with pancreatic juice and alkali juice of the intestines, together with fat present there, the dye is precipitated by the fat, and this precipitate is soluble in neither strong alkalies or strong acids, and casts a stronger shadow than if the dye were in solution. However, not all cases present roentgenograms with this finding after a fat meal, not even if they are taken at short intervals after the administration of fat. Is this an

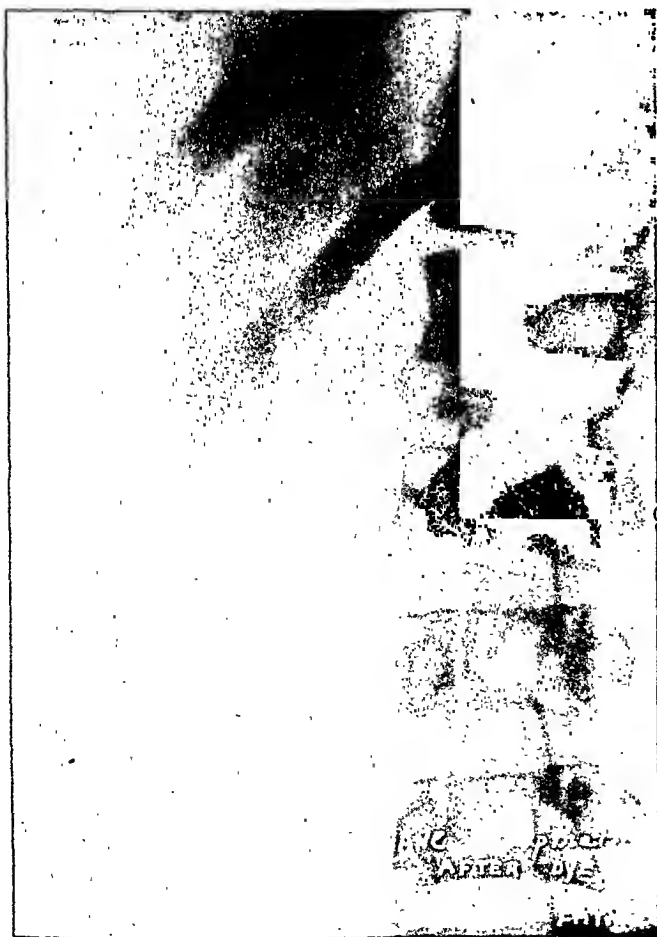


Fig. 17. Five minutes after a fat meal, the dye shadow appears in the cystic duct, common duct, and duodenum.

stimulate the liver cells to form more bile salts and other secretions, and these of course will keep the cholesterol which is formed in more abundance during periods of temperature and in starvation more in solution. During chronic disease, the patient should be forced to eat, especially of fatty food, because fat not only stimulates the liver to form more bile salts, but also keeps the gall bladder free from stasis.

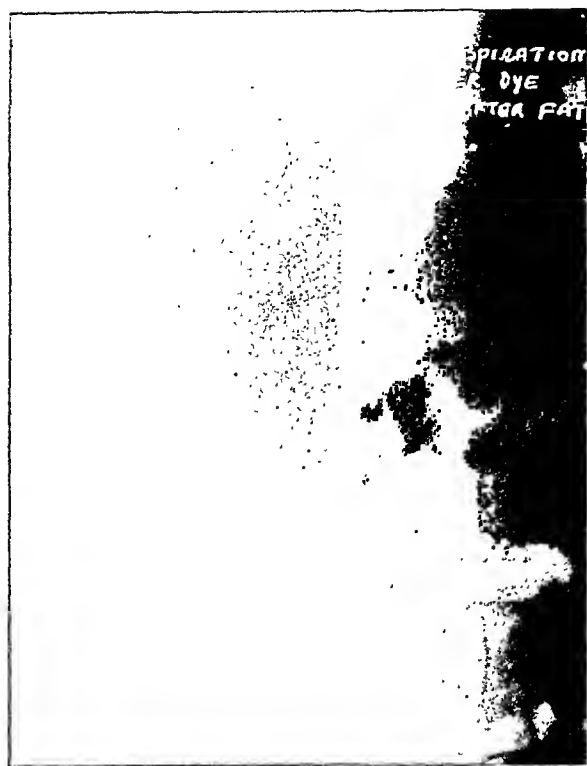


Fig. 19. Twenty-six minutes after a fat meal. There is still more dye in the duodenum, and even greater contraction of the gall bladder.

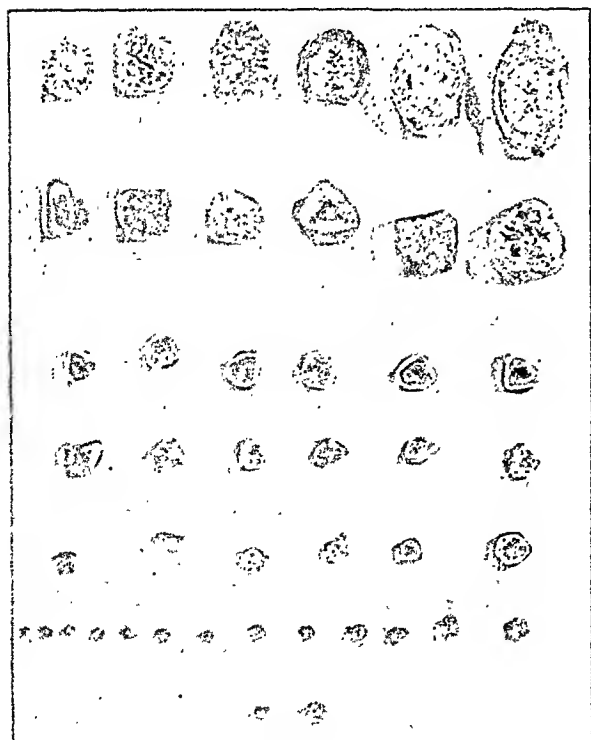


Fig. 20. A group of different types of gall stone.

TABLE 1

A. FACTORS WHICH TEND TO CAUSE AN ABNORMAL CONCENTRATION OF BILIARY CONSTITUENTS.

1. *Increased ingestion* (22).
2. *Increased elimination of biliary substances due to some pathological condition causing destruction of*
  - a. Cholesterol-containing materials in
    1. Central nervous tissues.
    2. Fatty structures.
    3. Blood corpuscles (14).
  - b. Calcium-containing structures in
    1. Bones, teeth, etc.
    2. Parathyroid disturbances.
  - c. Bilirubin-containing structures in
    1. Blood cells.
    2. Bone marrow.
3. *Liver disturbances causing excretion of bile with low bile-salt cholesterol ratio.*
  - a. Functional disturbances in sympathetic nervous system of liver as factor in pathogenesis of gall stones (12).
  - b. Liver poisons (32), (17).
  - c. Diseased livers (2).
  - d. Role of disturbances in sulphur metabolism (Taurine) in production of gall stones (27), (28).
4. *Disturbances in pancreatic secretion.*
  - a. Diabetes (3).
  - b. Formation of gall stones (26).
5. *Other glandular disturbances.*
  - a. Ovarian: pregnancy; increase in body weight.
  - b. Parathyroid.
  - c. Kidneys: relation of gall stones to renal disturbances (4).
6. *Gall bladder disturbances.*
  - a. Differential absorption of substances by mucosa of gall bladder in process of concentration of bile.
  - b. Increase in gall bladder excretion of
    1. Calcium in infection (23).
    2. Cholesterol excreted in
      - (a) Strawberry gall bladder (30), (8).
  - c. Factors causing stasis in gall bladder, or decrease in emptying time:
    1. Infections of gall bladder (Also cause absorption of bile salts) (5).
    2. Adhesions of gall bladder.
    3. Diverticula of gall bladder.
    4. Polyps, or cancer of gall bladder.
    5. Infections, etc. of common duct.
    6. Gastro-intestinal conditions affecting the Papilla of Vater by reflex action.
      - (a) Duodenal ulcers.
      - (b) Duodenitis.
      - (c) Appendicitis, etc.
  7. Starvation (20).

B. FACTORS CAUSING AN INCREASE IN TEMPERATURE ALLOW MORE BILIARY CONSTITUENTS TO BREAK DOWN, AND MORE BILIARY CONSTITUENTS TO GO INTO SOLUTION. AS THE TEMPERATURE FALLS THERE IS A TENDENCY FOR BILIARY CONSTITUENTS TO PRECIPITATE.



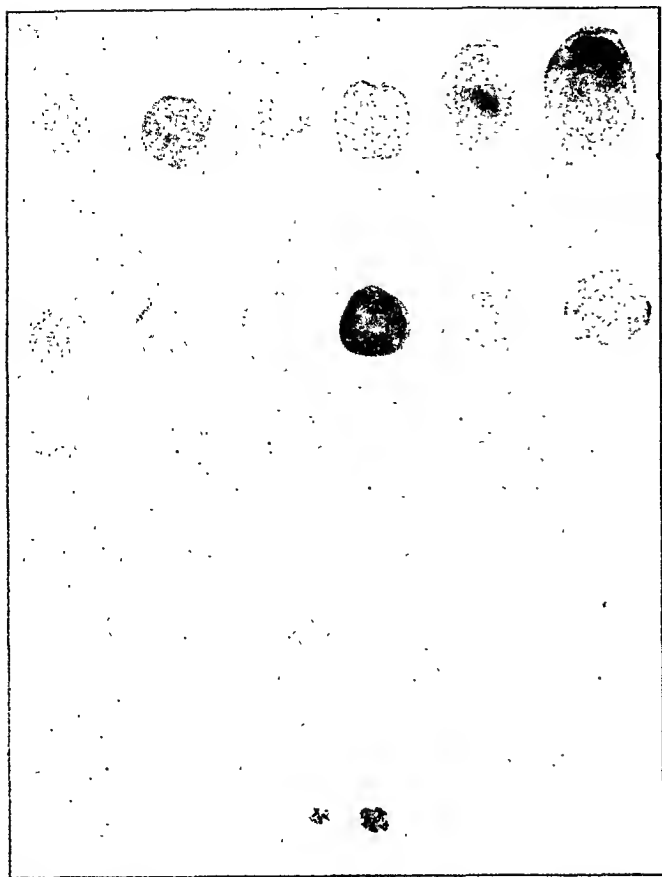


Fig. 21. Roentgenogram of the stones in Fig. 20 taken with moderate quantity of X-ray.

indication that in some gall bladders absorption of dye may occur as it does in a dog?

According to the figures of Ferguson and Palmer (11) in a grand total of 552 patients in which stones would probably be found, 15% would have stones which would cast a positive shadow, that is, stones in which calcium would form part, or all, of the shadow; 20% would have stones casting a negative shadow, that is, stones in which cholesterol was the major ingredient. These negative stones cast a negative shadow on the film, not only because of the dye around them, but also because they are usually faceted stones which have a hollow center, or a center containing fluid from which all crystallizable material has been precipitated.

In the remaining 65% in which stones would be presumably present, no shadow could be seen, and the gall bladder either did not fill with dye, or filled poorly, and the stones in these cases also, are cholesterol stones, or occasionally, pigmented stones. In this latter group the gall bladder did not fill with dye because it could not empty, for if the gall bladder cannot empty its old contents it also cannot be filled with new bile containing dye. It is also interesting to note in another series of cases that of the gall bladders which gave a faint shadow or no dye shadow at all, three-fourths contained stones.

By giving these patients a fatty meal and bile salts for several days before their gall bladder X-ray examination, a great many more of these stones can be brought out, because the majority of them are faceted. As a matter of fact even if no dye entered the gall bladder the very nature of these stones makes it

possible to visualize them, though I admit a great many more roentgenograms have to be taken, and technique must be greatly varied.

It has happened repeatedly in our roentgen-ray department that where gall stones were missed at the first visualization, they were found at the second. Figures 20, 21, and 22 show a series of different types of gall stones, and illustrate how it is possible, by giving too much X-ray, to go right through the stones without seeing them.

Now again, of what value is the information as to the type of stone present in a case as determined by the roentgenograms, or even as determined by the structure after removal?

First of all, one can focus his attention, if the stone is a cholesterol stone, upon the factors which are apt to produce cholesterol stones, even after removal of the gall bladder. If the stone is a calcium or a pigmented stone, the attention can be focussed upon the factors which produce these types of stone. After cholecystectomy all the biliary elements secreted by the liver are greater in amount than those coming down when a gall bladder is present. Bile coming from animals in which there is no gall bladder is also richer in all the elements than that in one in which there is a gall bladder. The reason that stones are not formed after cholecystectomy oftener because of this greater concentration of elements is, first, there is a dilatation of the ducts, a greater secretion, a quicker emptying time. The Papilla of Vater is dilated, and thus no

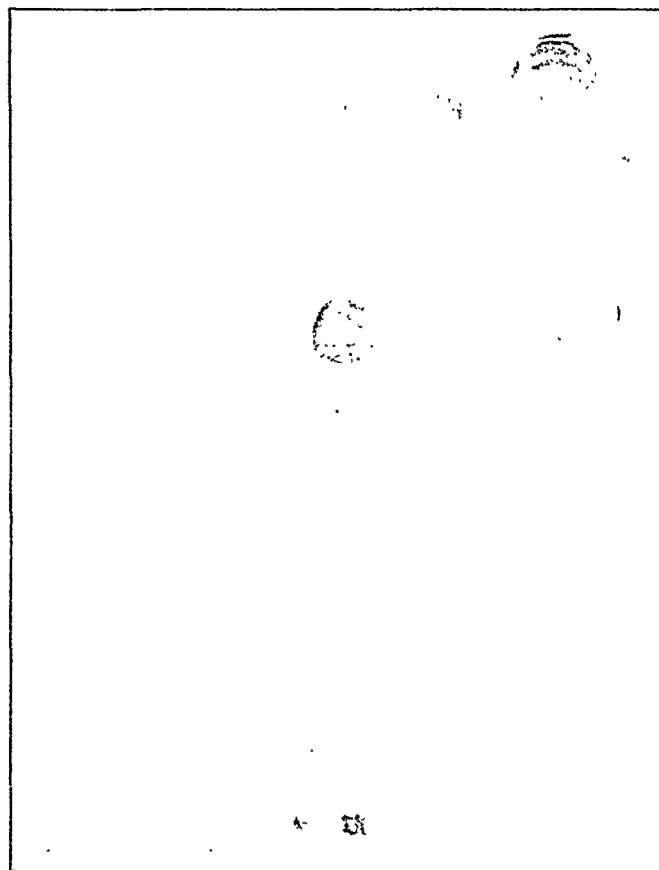


Fig. 22. The same stones as shown in Figs. 20 and 21. When the amount of X-ray is increased it actually goes through all the stones except those which contain a great deal of calcium.

stasis is allowed. Nevertheless, gall stones may form after cholecystectomy, either in what is left of the gall bladder, or in the rest of the biliary passage.

Cholecystectomy is not a 100% sure proof therefore,

that no more stones will form, and treatment should be started after operation which has a tendency to prevent precipitation of cholesterol or formation of the type of stone found at operation.

## REFERENCES

1. Andrews, Edmund; Schoenheimer, Rudolph, and Hrdina, Leo: Etiology of Gall Stones. *Arch. Surgery*, Vol. 25, No. 4, Oct., 1932.
2. Andrews, et al.: Etiology of Gall Stones and Analysis of Duct Bile, from Diseased Livers. *Ibid.*, Vol. 25, No. 6, p. 108, Dec., 1932.
3. Baemelster, Untersuchungen über cholesterinnusscheidung in menschlichen Gallen. *Biochem. Ztschr.*, 26:223, 1910.
4. Bilger, F., and Fontaine, R.: *Rev. de chir.*, Paris, 50:34, Jan., 1931.
5. Deaver, John B.: Etiology of Gall Bladder Disease. *Penn. Med. J.*, 33:13-15, Oct., 1929.
6. Delario, A. J.: Path of Absorption and Excretion of Sodium Tetraiodophenolphthalein. *The Jour. Lab. and Clin. Med.*, Vol. XVI, No. 4, Jan., 1931.
7. Delario, A. J.: Unusual Cholecystograms and their Interpretation. *Am. Jour. Roentgen. and Rad. Ther.*, Vol. XXIV, No. 5, Nov., 1930.
8. Elman, R., and Graham, E. A.: Pathogenesis of "Strawberry Gall Bladder." *Arch. Surg.*, 24:14, Jan., 1932.
9. Elton, N. W., and Deutsch, E.: Concentration and Precipitation of Bilirubin in the Gall Bladder and Bile Ducts. *Arch. of Path.*, 15:818, 1933.
10. Encyclopedia Britannica, Fourteenth Edition, Vol. 1, p. 739.
11. Ferruson, A. N., and Palmer, C. W.: Cholecystography. *J. A. M. A.*, Vol. 100, No. 11, p. 809, March 18, 1933.
12. Gaisvinsky, B. E.: *Ztschr. f. d. gen. exper. Med.*, 88:357, 362, 23.
13. Gaur, H., and Davis, C. L.: The Incidence of Gall Stones in Cattle. *J. of Am. Med. Assoc.*, 81:71, July, 1932.
14. Goodman, E. H.: Ueber den Einfluss der Nahrung auf die Ausscheidung von Gallensnuren und cholesterin durch die Galle. *Beitr. z. chim. Physiol. u. Path.*, 9:91, 1907.
15. Hammersten, O.: A Text Book of Physiological Chemistry, 4th Ed., H. L. Chapman and Hall, Ltd., London, p. 282.
16. Hnrlie, D. J.: The Formation of Gall Stones. *Brit. Med. Jour.*, 1:153, Feb. 3, 1934.
17. Kusumoto, C.: Ueber den Einfluss des Toluylendiamins auf die Ausscheidung Gallen. *Biochem. Ztschr.*, 26:223, 1910.
18. Matthews: Physiological Chemistry, 3d Ed., Wm. Wood & Co., p. 416.
19. Mounther and Sulder: Cited from Text Book of Physiological Chemistry, Matthews, p. 85, Wm. Wood & Co., New York, 3d Ed., 1920.
20. McMaster, P. D.: Studies in Total Bile. *J. Exp. Med.*, 40:25, 1924.
21. Mentzer, Stanley H.: The Status of Gall Bladder Surgery (based on a study of 14,000 specimens). *J. A. M. A.*, Vol. 90, No. 8, pp. 607-610, Feb. 25, 1928.
22. Mentzer, Stanley H.: Cholecystic Disease in Pigs, Sheep, and Cattle. *Colif. and Western Med.*, 40:333, May, 1934.
23. Phemister, Dallas B.; Day, L., and Hastings, A. B.: Calcium Carbonate Gall Stones and Their Experimental Production. *Ann. Surg.*, Vol. XCVI, No. 4, p. 595, Oct., 1932.
24. Ravdin, I. S.; Riegel, C.; Johnston, C. G., and Morrison, P. J.: Biliary Tract Disease. *J. A. M. A.*, Vol. 103, No. 20, p. 504, Nov. 17, 1934.
25. Sweet, J. E.: Luesegang Phenomenon in Gall Stones, *Colloid Symposium Annual*, 1930.
26. Sweet, J. E.: Formation of Gall Stones. *Ann. Surg.*, 99:392, Feb., 1934.
27. Tonaka, A.: Role of Disturbances in Sulphur Metabolism in Production of Gall Stones. *M. H.*, a. d. med. akad. su, Koto, 7:328-33.
28. Tonaka, A.: Role of Disturbances in Sulphur Metabolism in Production of Gall Stones. *Zr. Jap. Path. Soc.*, 21:88, 31.
29. Tutton, A. E.: The Natural History of Crystals, Paul Kegan, Trench, Trubner and Co., Ltd., London, 1924.
30. Wilkie, A. L., and Doughton, Henry: Passages of Cholesterol Through Mucosa of Gall Bladder. *Arch. Surg.*, Vol. 26, No. 1, Jan. 3, 1910.
31. Willstaetter: Cited from Physiological Chemistry, Matthews, 3d Ed., Wm. Wood & Co., p. 414.
32. Wipple, G. H.: Bile Salt Metabolism. *J. Bio. Chem.*, 59, 623, 1924.

## Abdominal Pain as a Misleading Symptom of Spinal Cord Lesions\*

By

EVERETT D. KIEFER, A.B., M.D.

BOSTON, MASSACHUSETTS

IN many cases of tumor of the spinal cord the earliest and most outstanding symptom is pain caused by irritation of the posterior nerve roots. When pain is present for considerable time before the onset of sensory and motor disturbances (which result from cord compression), its cause may be thought to lie in the region supplied by the affected nerve, thus leading to gross errors in diagnosis. When the cord lesion is situated at some level between the 7th and the 12th thoracic segments, abdominal pain may occur and frequently results in fruitless abdominal surgery.

Spinal tumor is not a common disease. Tumors involving the cord are considerably less frequent than intracranial tumors. Nevertheless, the condition is not rare, and it has been said (1) that in about ten per cent of cases serious diagnostic errors are made before the true nature of the complaint is suspected. In almost every reported series of cord tumor cases there is listed one or more patients who has undergone abdominal operations for pain which was finally found to be produced by irritation of spinal

nerves. It is evident, therefore, that this condition is worth consideration in abdominal diagnosis.

The condition known as "cord bladder" is well recognized as a complication of spinal cord disease. Similarly, constipation is almost universal in cases of cord tumor because of disturbances of the rectal reflexes. For example, a patient with a cord lesion presented herself to the gastro-intestinal department of this Clinic with the chief complaint of obstinate constipation. This patient would go for several days with the rectum distended with soft feces but experiencing no inclination to go to stool. Usually the bowel disorder is troublesome and difficult to overcome. As cord compression increases, incontinence of feces develops, but by this time there may be other definite neurological disturbances which indicate the nature of the trouble.

A complete survey of the literature has not been attempted, but one of the most striking cases of abdominal pain arising from a cord lesion is found in Elsberg's book (2) on spinal cord tumors. This patient was a woman, aged 36, who for two years had had attacks of pain in the right hypochondrium and back. The gall bladder containing stones was removed without relief. The pain spread to the right lower quad-

\*From the Department of Gastro-enterology, Lahey Clinic. Read before the 35th Annual Session of the American Gastro-enterological Association, Atlantic City, N. J., June 10-11, 1935. Approved by the Publications' Committee of the Association.

rant and an appendectomy was performed without relief. Later she was operated upon for right inguinal hernia, again without relief. Definite motor and reflex disturbances developed and a subsequent laminectomy disclosed a tumor compressing the right 5th, 7th and 8th thoracic posterior roots.

Frazier and Spiller (3) have reported the case of a woman aged 52, who 5½ years before examination had complained of burning pain in the epigastrium and vomiting without relation to meals. Although the vomiting subsided the pain persisted with some radiation to the left and was usually worse at night. Her bowels were extremely constipated. Neurologic examination, however, indicated a spinal lesion, and at operation there was disclosed a tumor at the level of the 7th thoracic vertebra.

Beckman (4) has reported the case of a patient with intermittent attacks of pain in the gall bladder region and vomiting. A cholecystectomy had been performed without relief before it was finally determined that the pain was caused by a tumor pressing upon the right 7th dorsal root.

A representative case which has come under our observation is that of a girl, aged 21, who came to this Clinic complaining of intermittent attacks of pain in the right upper quadrant of the abdomen over a period of two years. The pain was aggravated by sudden twisting of the neck, also by coughing but was not associated with nausea or vomiting. There was marked constipation but no bladder symptoms. There had been a slight sensation of stiffness in the right leg for two weeks.

There was tenderness in the right lower quadrant. The deep reflexes of the lower extremities were hyperactive particularly on the right. A bilateral Babinski reflex was present. Very slight hyperesthesia was present in the right first and second lumbar skin areas. Vibratory sense was slightly diminished on the right. The spinal fluid was slightly xanthochromic. A laminectomy by Dr. Horrax revealed a neurofibroma at the level of the seventh thoracic vertebra.

Rectal pain simulating that caused by rectal disease may be produced by tumors of the cauda equina. An instance of this is reported in Elsberg's book (2) in the case of a woman, aged 43, who had complained of rectal pain over a period of 12 years. Operations including hemorrhoidectomy, removal of the coccyx, division of the sphincter ani, sigmoidopexy and suspension of the uterus had been performed without relief. At the time of the neurologic examination there was also pain in the lower extremities, bladder control was lost at times and the rectal pain was accentuated by lying down. There was only slight weakening of the reflexes and slight diminution of sensation in the lower limbs, but a laminectomy revealed a tumor at the level of the first sacral vertebra.

A similar case from our series was a man, aged 41, who came to this Clinic complaining of pain in the region of the sacrum and severe constipation of three and a half years' duration. The pain was aggravated by lying down. For about four months he had had some difficulty in emptying his bladder.

There was tenderness over the lumbosacral spine. The knee jerks and ankle jerks were absent. The abdominal reflexes were absent on the right side. There was some loss of sensation around the rectum and along the left thigh.

A laminectomy by Dr. Horrax disclosed a tumor extending from the level of the 10th dorsal vertebra to the 3rd lumbar vertebra which proved to be an ependymoma of the cauda equina.

Spinal lesions other than tumor may be productive of abdominal pain through pressure on appropriate nerve roots. These include compression fractures of vertebra, tuberculosis of the spine, hypertrophic arthritis and herniation of the nucleus pulposus, and chronic spinal arachnoiditis.

Chronic arachnoiditis is another condition which if present in the spinal canal may act as a tumor equivalent, giving rise to almost identical clinical pictures with the same difficulties in differential diagnosis. This condition has been recognized for many years as a definite pathological entity characterized by thickening of the arachnoid membrane, engorgement of the pial blood vessels and the formation of dense adhesions in the subdural space. Little is known of its etiology. Because of the tendency to recurrence the surgical treatment of chronic arachnoiditis is less satisfactory than that of cord tumors, but the relief derived from the division of subdural adhesions or of the sensory nerve roots may persist a long time making operative interference well justified.

#### ARACHNOIDITIS CASE REPORTS

In this Clinic three patients have been examined for abdominal pain arising from chronic spinal arachnoiditis verified by laminectomy.

*The first case* was that of a man, aged 43, who, two years previously had begun to have pain in his upper right back. The gall bladder which contained gall stones had been removed without relief. Later, because of continued attacks of upper abdominal pain resembling biliary colic, the common duct had been explored. No stones were found and no relief followed the operation. A third operation had been performed at which time periduodenal adhesions were found and separated but the pain remained unrelieved. At no time were there definite motor, reflex or sensory disturbances but because of increased protein content of the spinal fluid, he was referred to this Clinic for laminectomy by Dr. Horrax. Freeing of arachnoid adhesions and division of the seventh pair of sensory roots gave relief.

*The second case* was that of a girl, aged 15, who came to this Clinic complaining of pain in the epigastrium and right abdomen with constipation of two months' duration. There was extreme tenderness of the epigastrium and of the right lower quadrant. An appendectomy did not relieve the pain or tenderness and urinary retention developed after the operation. Neurologic examination showed hyperesthesia on the right side up to the 12th thoracic vertebra, atrophy and slight loss of power of the right leg, hyperactive reflexes with a questionable Babinski of the left lower extremity and slight loss of vibratory sense on the right side. Abnormalities in the spinal fluid dynamics and in the lipiodol studies indicated disease in the subdural space. At laminectomy freeing of arachnoid adhesions between the levels of the 8th and 12th thoracic vertebrae gave relief of symptoms.

*The third case* was a girl, aged 17, who came to this Clinic complaining of intractable constipation and pain in her right side of six weeks' duration. For a year she had had pain in the lower back. Her appendix had been removed without relief of pain or of constipation. Physical examination showed exaggerated tenderness in the right lower quadrant. The rectum was dilated and filled with soft feces. The temperature and white blood count were slightly elevated. While she was under observation it was noted that she was incontinent of urine at night and

occasionally there was urinary retention requiring catheterization. The knee jerks were absent. There were some vasomotor disturbances in both lower extremities, some loss of sensation to pain, touch, temperature and vibration over the left lower extremity. The extensor muscles of the left foot and left thigh were weak.

The spinal fluid was slightly xanthochromic and lipoidal studies appeared to localize a lesion at the level of the 7th thoracic vertebra.

At laminectomy performed by Dr. Horrax, the arachnoid was found to be gray, thickened and adherent.

Following the operation the pains were relieved and the bowel function became normal. Two months later she again had to resort to small enemas to initiate the act of defecation but her course was satisfactory until a year after the operation when she developed mild fever, pain in the right arm and right back and increasing constipation. When conservative measures did not relieve her, a second laminectomy was performed with the separation of additional arachnoid adhesions resulting in relief of pain and return to normal bowel function.

The fact that abdominal pain resulting from dorsal root irritation may be unilateral, that it may occur in sharp intermittent attacks and that it may be associated with vomiting, constipation or urinary tract symptoms, makes the similarity to visceral disease striking and misleading. However, there are certain differential characteristics of this symptom which when properly elicited and recognized should serve adequately to arouse suspicion as to its true nature. If the pain has definite localization and persists for several months or longer without variations except in degree, spinal tumor should be thought of as a possible diagnosis. Pain which is induced or aggravated by sneezing, coughing, grunting or lying down and which is relieved by the sitting position, is particularly suggestive. Although root pain may appear first, pain in the lower back and in the lower extremities usually develops when the tumor increases sufficiently in size to cause pressure upon the spinal cord (5). Girdle sensation, a third type of pain associated with cord tumors is described as a sensation of a tight cord about the trunk. Therefore, when abdominal pain is accompanied by pain in the lower back and lower extremities or by girdle sensations, its diagnostic significance becomes more apparent.

Pain with the above characteristics indicates that a search should be made for motor, reflex and sensory disturbances. Although it is true that in a large proportion of the reported cases such changes were present when the laminectomy was performed, it is impossible to determine just when, in the usually long history of pain, objective neurologic signs appeared. Nevertheless it seems probable that if attention could be focused upon the central nervous system and appropriate examinations carried out, earlier diagnoses would be possible.

On examination of the patient there may be hyperesthesia or hypesthesia in the region of the pain but it is not a constant finding. As cord compression develops lively tendon reflexes, ankle clonus or plantar extension may be elicited. If there is found diminution in the pain and temperature sensations over the lower extremity on the opposite side from the pain, the diagnosis is fairly definite. However, it is more common to find slightly diminished sensation on both sides below the suspected level.

Sphincter disturbances, although not usually the earliest manifestations, may complete the clinical

picture in such a way as to lead to the correct diagnosis. The usual sequence of bladder disturbances is frequency, hesitancy, retention and incontinence.

## CASE REPORTS

### *Case No. 1.—Neurofibroma at the level of the seventh thoracic vertebra (6).*

M. S., a girl, aged 21, unmarried, came to this Clinic complaining of pains on the right side of the abdomen, which had been present intermittently for two years with no associated nausea or vomiting. At first the pains were located mainly in the right upper quadrant. A gall bladder visualization showed normal function. The pains were aggravated by sudden twisting or bending of the neck and also by coughing. There was marked constipation but there were no bladder disturbances. There was a slight feeling of stiffness in the right leg for about two weeks previous to her entrance to the hospital. The rest of the history was irrelevant.

Physical examination showed moderate superficial and deep tenderness in the right lower quadrant. The abdominal reflexes were brisk and equal. The patellar and Achilles reflexes on the right were markedly hyperactive (///) and slightly less active on the left (/). A bilateral Babinski reflex was present. A very slight relative hypesthesia could be detected over the first and second lumbar skin areas on the right. Vibratory sense over the right internal and external malleoli was slightly diminished. The lumbar puncture showed an initial pressure of 120 mm. of water. Prolonged jugular compression brought an immediate rapid response, the fluid rising rapidly to 260 mm. and descending with the same speed on the release of the jugulars, the patient breathing normally throughout the procedure. The fluid, when compared with water, was slightly tinged with yellow. The total protein of the spinal fluid was 60 mm. per hundred cubic centimeters. Iodized poppy-seed oil injected into the cisterna twenty-four hours later stopped at the seventh thoracic vertebra; a few drops of the oil passed the obstruction after several hours. A laminectomy revealed a firm neurofibroma which was large enough to cause a pressure furrow in the spinal cord. There were no adhesions.

### *Case No. 2.—Ependymoma of the Cauda Equina.*

Mr. E. P. Clinic number 34157, male, age 41, came to this Clinic June 22, 1933, complaining of "arthritis" and constipation. For three and a half years he had had pain in the region of the sacrum and the sacro-iliac joints, for which he had worn a belt and had had most of his teeth removed without any relief. For five or six years he had increasingly severe constipation which seemed to aggravate the pain in the lower back. He was unable to sleep in bed and most of the time slept in a chair. The constipation had become so severe that it required a laxative after every meal. The stools were normal except for some mucus. There was some bloating but no marked abdominal distention. For about four months he had noticed increased difficulty in micturition. There was no complete stoppage at any time but the stream had become smaller and at intervals there was some difficulty in voiding.

The general physical examination was negative except for tenderness to palpation over the lumbosacral spine, with considerable limitation of motion of the lumbar spine. The knee jerks and ankle jerks were not obtained. There was no Babinski reaction or ankle clonus.

X-rays of the lower spine and sacro-iliac region showed asymmetry of the lumbosacral articulations. The posterior portion of the first sacral vertebra was not closed in. An X-ray examination of the colon by means of a barium enema was not remarkable except for some spasm of the left side of the colon and some dilatation of the right side. There was complete evacuation of the enema. Other laboratory work, including urine, blood counts, blood Wassermann, blood sugar, blood non-protein nitrogen, comple-

ment fixation test for gonorrheal infection, was normal. Gastric analysis showed free hydrochloric acid of 45.

On admission to the hospital the patient developed urinary retention with distention of the urinary bladder and it was found to be very difficult to get his bowels to move. On cystoscopic examination a diagnosis of a cord bladder was made. A neurological examination showed absent knee jerks and ankle jerks, no Babinski or ankle clonus, absent cremasteric reflexes, abdominal reflexes present on the left side but absent on the right. There was some loss of sensation around the rectum and along the left thigh.

Lumbar puncture was performed but no fluid was obtained in the 3rd, 4th and 5th lumbar spaces or the first sacral. Intrathecal injection of lipiodol showed a definite block at the level of the 10th dorsal vertebra.

A laminectomy by Dr. Horrax and Dr. Poppen disclosed a tumor extending from the level of the 10th dorsal vertebra to the 3rd lumbar vertebra which proved to be an ependymoma of the cauda equina. The large tumor was completely removed.

The patient's convalescence was not remarkable. Seventeen months after the operation the patient's condition was improved but he still had some difficulty in walking and had some pains in his legs.

#### *Case No. 3.—Localized spinal arachnoiditis.*

Miss D. S., case number 37597, female, aged 15, came to this Clinic on January 9, 1934, complaining of pain in the epigastrium and in the right side of the abdomen of two months' duration. There was no vomiting but considerable nausea. Food taken aggravated the pain and caused considerable gaseous eructation. The pain was sharp in character, was more severe in the upper abdomen and did not radiate down the back or into the extremities. About one year previously she had had severe back pain for a few weeks thought to be due to wrenching of her back while doing exercises in a gymnasium. She complained of constipation but had noted no bladder difficulty and complained of no sensory or motor disturbances.

Physical examination was not remarkable except for extreme tenderness and hyperesthesia of the epigastrium and the right lower quadrant of the abdomen. The slightest touch caused wincing.

Gastro-intestinal X-rays by means of a barium meal and a barium enema showed no organic disease. The colon was dilated and redundant throughout and the barium enema was not well evacuated. It was noted in the X-ray films that the urinary bladder was apparently dilated. Because of the short history and the localized tenderness in the right lower quadrant an appendectomy was advised and carried out. The appendix showed no signs of acute inflammation and the exploration of the abdomen at the time of the operation was negative except that the urinary bladder was distended. Spinal anesthesia, metyaine, was used.

Because of persistent abdominal pain and tenderness after the operation and persisting urinary retention to the extent that on the ninth postoperative day there were forty-eight ounces of urine in the urinary bladder, a neurological examination was carried out. The positive findings were regions of hypesthesia on the right side up to the 12th thoracic vertebra; definite atrophy and loss of power of the right leg; hyperactive reflexes of the left lower extremity but no clonus; questionable Babinski on the left side; vibratory sensation diminished over the right external and internal malleoli; slight change in position sense.

A combined cisternal and lumbar puncture showed markedly differing pressures in the lumbar and the cisternal regions, indicating a complete block of the subarachnoid space. Lipiodol injected into the cisterna passed down into the sacral canal in two hours with the exception of two or three drops which stayed at the level of the 12th thoracic vertebra. When the patient was placed in a marked Trendelenburg position the lipiodol moved rapidly until it

reached the level of the 12th vertebra, then stopped for a few seconds and then kept going upward in a small, thin stream and again stopped completely at the 9th thoracic vertebra.

On February 1, 1934, a laminectomy was performed by Dr. Gilbert Horrax and Dr. James Poppen, which showed localized arachnoiditis involving the cord from approximately the 8th thoracic vertebra to the 12th. The arachnoid adhesions were freed.

The postoperative course was uneventful. The abdominal pain and tenderness cleared up. The function of the bowel and the bladder became normal and up to the present time she has had no recurrence of her symptoms. Diagnosis: Localized subarachnoiditis at the level of the 8th to the 12th thoracic vertebra.

#### *Case No. 4.—Localized spinal arachnoiditis.*

Mr. H. C. T., Clinic No. 44555, male, age 43, registered at this Clinic December 4, 1934. The patient had been in excellent health until four and one-half years ago, when after stooping over he was seized with a sudden severe pain in the middle of the back. He practically collapsed but was able to be up and about with difficulty after several days. He was quite well except for some low back pain until 1932, when he complained of abdominal discomfort and pain in the upper right back occurring in attacks. A cholecystogram showed gall stones and in December, 1932, a cholecystectomy was performed.

However, the pain was not relieved after the operation and in June, 1933, an examination of the spinal fluid by means of a combined cisterna and lumbar puncture showed increased protein; 78 mgs. in the lumbar region and 34 mgs. in the cistern fluid, indicating some disturbance in the flow of cerebrospinal fluid, although no definite dynamic block was demonstrated. Lipiodol injected into the cisterna flowed downward normally except for deviation of the stream to the left at the level of the 3rd and 4th dorsal vertebrae.

Because of continued attacks of upper abdominal pain resembling biliary colic and because the abdomen was more suspicious as cause of the pain, a second operation was performed in July, 1933, for possible common duct stone. There was no jaundice.

At the operation many periduodenal adhesions were encountered but no stones were palpated in the common duct.

The pain was still unrelieved and in October, 1933, X-ray examinations showed partial obstruction of the jejunum.

He was again operated upon, the obstructing adhesions were broken up and the common duct was opened and explored. No stones were found.

The pain was still unrelieved and the patient had become to depend more and more upon opiates. In April, 1934, orthopedic treatment was instituted although the only finding was a rather sharp lateral curvature in the upper dorsal region.

Since there was no satisfactory relief from this he was referred to Dr. Gilbert Horrax for exploration for a probable intraspinal lesion. There were no bladder or rectal symptoms. The blood and spinal fluid Wassermanns were negative. Neurologic examination showed no sensory or motor disturbances except increased deep reflexes throughout.

At operation by Dr. Horrax and Dr. Poppen, the dorsal laminae from the 5th to the 9th were removed. The arachnoid was distinctly thickened and opaque and when this membrane was opened there was seen to be a meshwork of adhesions from it to the underlying cord throughout the whole extent of the area exposed, but was particularly dense in the region of both of the 7th sensory roots and the 8th on the right side. The adhesions were freed as much as possible and the 7th pair of sensory roots were divided.

The postoperative course was uneventful and the symptoms have been entirely relieved.



*Case No. 5.—Diffuse generalized chronic arachnoiditis.*

Miss M. G., Clinic No. 36193, female, age 17, was registered in the gastro-intestinal department at this Clinic October 13, 1933, complaining chiefly of severe constipation and pain in the right side.

The patient had been totally deaf since birth but appeared to be of average intelligence and could read lips fairly well and speak a few words. She was a full term baby and delivery was without instruments. Since birth she had been troubled with constipation and moderate abdominal distention. Enemas and laxatives had been used throughout her life.

For about one year she had complained of low back pain. About six weeks before admission she began to have pain in her right side of the abdomen associated with frequent vomiting. After about ten days her appendix was removed without relief of pain. Because of the severe constipation she was kept in the hospital for four weeks, during which time she lost weight and showed no improvement in bowel function. Even with enemas she would go as long as 11 days without having a stool. For about a week before coming to this Clinic, she had been urinating in bed while asleep.

Physical examination showed her to be rather poorly developed and poorly nourished. There was tenderness in both lower quadrants particularly in the region of the appendectomy scar. However, the tenderness appeared to be superficial in the nature of marked skin hyperesthesia. There was slight scoliosis of the lower dorsal spine. The rectal examination showed a large rectum distended with soft feces. The knee jerks were present and equal. Blood pressure 115/70. Weight 91 lbs.

The laboratory tests showed the urine to be normal. The red count was 5,170,000, the white count 8,200 and the hemoglobin 87%. The gastric analysis showed a free acidity of 15 after an Ewald meal. The blood Wassermann was negative.

A barium enema filled the colon slowly with some distress to the patient. The colon was moderately redundant and only slightly dilated. The rectum was filled with a large amount of fecal material.

She was treated in the hospital from October 28, 1933, until November 17, 1933. During this time she had a slightly elevated temperature scarcely ever over 100° F. The white count was 13,000. She complained considerably of pain in her back and of headache. The bowel function remained sluggish and it was noted that bowel action appeared to be normal but the feces accumulated in the rectum without producing a desire to defecate. However, very slight stimulation of the rectum produced a normal movement. There was some bed wetting in the hospital but this stopped before discharge.

A neurological examination by Dr. Gilbert Horrax showed both elbow reflexes present. The knee jerks could not be obtained. Achilles jerks active on both sides. Abdominals present and active on both sides. The planter responses were normal, no ankle clonus. There was slightly less strength in the left leg than the right. The optic fundi were normal. There was some hyperesthesia of the left leg but it did not coincide well with the anatomical nerve distribution and was more characteristic of a "stocking" type of anesthesia. A spinal puncture was advised but was not done until her second admission December 16, 1933, when she was readmitted with acute urinary retention. A cystoscopy with a right pyelogram was negative.

A neurologic examination showed absent knee jerks, some vasomotor disturbances in both lower extremities, some loss of sensation to pain, touch, temperature and vibration of the left lower extremity, and definite weakness of the extensor muscles of the left foot and left thigh. She still complained of pain in the right back and down the left leg.

A lumbar puncture showed slightly xanthochromic spinal fluid with no change in pressure with jugular com-

pression, coughing or straining. The spinal fluid Wassermann and gold sol reactions were negative. The total protein of the fluid was 60 mgs. per 100 c.c.

Following the lumbar puncture the pain was accentuated. There was a definite level of hyperesthesia corresponding to the 9th rib on the left and a region of hyperesthesia on the right involving the 11th and 12th thoracic segments.

Lipiodol injected into the lumbar subarachnoid space rose to the level of the 7th thoracic vertebra where it appeared to be definitely obstructed. There were scattered drops of iodized oil scattered along the spinal canal below this suggesting chronic arachnoiditis.

On December 20, 1933, Dr. Horrax and Dr. Poppen performed a *laminectomy*, removing the laminae from the 4th to the 8th thoracic vertebrae. The arachnoid was found to be pale gray and thickened. It was adherent to the pia by means of a diffuse mesh of adhesions. These adhesions were broken up and a small, soft rubber catheter was passed both upward and downward in the spinal canal showing no additional obstruction.

The postoperative convalescence was uneventful. Her bowel function and bladder function became entirely normal and remained so for about two months, when she again found it necessary to stimulate the rectum with a small enema in order to have a movement. Repeated examinations of the rectum showed the rectum filled with soft feces. There were no hemorrhoids, fissures or other disease of the anal canal. For several months she showed a slight elevation in temperature but was comfortable except for occasional pain in the back and right leg. In September, 1934, her weight was 99 lbs.

In December, 1934, she was readmitted to the hospital with an indefinite acute infection which apparently aggravated the arachnoiditis causing pain in the right arm and back, with vomiting. There was some hyperesthesia of the entire right side below the neck with the exception of the leg and forearm. Conservative measures failed to relieve the root pain and a second laminectomy was performed at the level of the 9th to the 12th thoracic vertebrae. The posterior roots were markedly involved in adhesions which were separated and the right 10th posterior root was divided because it was so extensively involved. A small mass of fibrous tissue measuring 3 cm. by 2 cm. and 4 millimeters in thickness was removed from the left side of the subdural space at the level of the 10th thoracic vertebra.

She was discharged from the hospital having no pain and with the bowel function returned to normal. About two months later there was some recurrence of pain in the right side accompanied by epistaxis, vomiting and constipation.

## SUMMARY

Clinical reports of several cases of spinal cord lesions have been presented in order to point out that such lesions, through irritation of posterior nerve roots, may produce abdominal pain which is easily confused with that caused by visceral disease. Particular attention is called to the condition known as chronic spinal arachnoiditis as a causative factor and to the fact that its presence may and frequently does lead to fruitless abdominal surgery.

Certain features of abdominal pain caused by spinal lesions should serve to arouse suspicion as to its true nature. These features are persistence in a definite location over a long period of time, aggravation by changes in body position, increase in pain by sneezing or coughing and association with pain in the lower back or lower extremities or with girdle sensation about the trunk.

Mistakes in diagnosis can be avoided by proper appreciation of these characteristics and by examining



the patient for motor, reflex and sensory disturbances which, although usually not marked, are frequently present.

### REFERENCES

1. Tamaki, K.: Thirty-nine Extramedullary tumors of the spinal cord. *Amer. J. Surg.*, 22:397, Dec., 1933.
2. Elsberg, C. A.: Tumors of the Spinal Cord, 1925. Paul B. Hoeber, Inc., New York, pp. 55 and 149.
3. Frazier, C. H., and Spiller, W. G.: An analysis of 14 consecutive cases of spinal cord tumor. *Arch. Neurol. and Psychiat.*, 8:455.
4. Beckman, E. H.: Tumors of the spinal cord with a report of 15 cases. *Journal-Lancet*, 37:35, 1917.
5. Ayer, J. B.: Symptoms and signs of tumors involving the spinal cord. *New Eng. J. Med.*, 203:295, Aug. 14, 1930.
6. Previously reported by Poppen, J. L., and Hurxthal, L. M.: Normal cerebrospinal fluid dynamics in spinal cord tumor suspects. *J. A. M. A.*, 103:391, Aug. 11, 1934.

### DISCUSSION:

DR. HOWARD F. SHATTUCK (New York City): We are certainly all indebted to Dr. Kiefer for his interesting and important paper. The conditions he described are not common, but he has made it clear that they may become pitfalls to any of us at any time. For a number of years we have been taught to look carefully to the heart, for example, in patients with acute symptoms in the abdomen.

Dr. Kiefer has forcibly reminded us not to forget the spinal cord. In short, as our President reminded us this morning, we must be competent internists, not to say neurologists perhaps, if we would attain competency in the medical specialty of gastro-enterology.

I was impressed with the length of time it takes to make a diagnosis in some of these patients. It is true some of them could be spared unnecessary abdominal operations if neurological signs and symptoms were looked for and recognized, but some of the patients apparently have their abdominal pain for a long time before the neurological symptoms appear, so I suppose that an occasional unnecessary abdominal operation seems inevitable. The important thing is to think of spinal cord involvement and to look for it.

I was also interested in the cases of chronic arachnoiditis that Dr. Kiefer described. The first of his series did not show the presence of any motor sensory or reflex disturbances, merely an increase in the protein content of the spinal fluid.

I should like to ask what are the minimal findings that should lead to an exploratory spinal operation in these cases.

DR. TEMPLE FAY (Philadelphia): Dr. Kiefer's paper emphasizes an experience common to most neurosurgeons. The time required to administer the anesthetic for these fruitless operations would be all that is necessary to establish the error in diagnosis, were the appropriate neurological tests carried out. In suggesting a greater familiarity with early neurological manifestations, it seems reasonable to expect that certain tests for neurological continuity should be routinely employed by the internist, in conjunction with the elaborate gastro-intestinal studies usually carried out:

(1). *Deviation and eversion* of the foot occurs as an important early motor sign of cord compression. With the patient placed flat upon the back, the position of the foot should be almost vertical in the normal, eversion of the foot occurs long before Babinski, clonus or weakness appear.

(2). *Babinski reflex* should be tested by carefully scratching over the outer border of the sole of the foot, using minimal stimuli, so as not to disturb the patient, thus frequently eliciting an early manifestation which otherwise might be concealed in a larger response when this reflex is carelessly or too energetically tested.

(3). *Gnostic sense* or the patient's ability to translate skin writing clearly, should be employed over the lower extremities, and numbers from one to ten quickly written on the skin surface by means of the finger or pencil, test not only serial tactile impressions to the skin, but include

two-point discrimination as well as visual projection of sensation into numerical concepts. This is not only a delicate test for all of the posterior column function of the cord, but determines whether or not the parietal lobe of the brain and visual-speech and motor-speech centers are intact and unimpaired.

(4). *The testing of pain and temperature responses* in the region of the buttocks and about the rectal area, is most important in that early sensory disturbances are elicited at this point, long before they appear on the body surfaces, from lesions producing a cord compression. This is due to the fact that the pain and temperature fibers for the gluteal area lie close to the surface of the cord, on its anterolateral borders. Compression of the cord produces disturbances of these superficial fibers before the deep tracts become involved.

(5). *The level of pain reference* should be carefully traced on the body by the patient and indicated with a skin pencil. The patient should be placed between the examiner and the daylight from a window so that the exposed skin surfaces may be observed from a distance. The light reflex given off from the portions of the skin where the nerve root involvement is present will appear slightly blushed and velvety, whereas, the skin above and below the level of root involvement will show a high glossy sheen. If this zone is carefully marked by a skin pencil and subsequently tested with pin point, heat and cold, hyperalgesic or disturbed sensory phenomena in this area will frequently indicate direct nerve involvement.

(6). *Scratching the skin* from below upward and crossing the zone of vasomotor disturbance noted above will frequently bring forth responses of hyperalgesia and definitely indicate the transition from a zone of hyperesthesia to the normal. Observing the red line produced by the scratch a few minutes later may indicate a wheel-like formation in the band of vasomotor instability. The vasomotor sign is a distinct root irritative phenomenon.

(7). *The sweating reflex* may be elicited by giving one-sixth of a grain of pilocarpin after surrounding the patient with warm blankets and noting the areas of sweating. Sweating occurs freely above the level of the lesion of the cord, disappearing below this point, or is inadequate. If a cord lesion is present, sufficient to give rise to the symptoms which Dr. Kiefer has described, there should be no question about delaying any thought of intra-abdominal surgery until the neurological examination has been carried to a complete interpretation of the findings noted above.

I could relate eight instances in my own experience where abdominal operations have been fruitlessly performed for spinal cord tumors. I believe, however, that the following instance proves not only an exception to this rule, but represents a triumph for the internist. Last Monday I operated a female patient, age fifty-one, who had complained of epigastric pains and weakness for the past three months. The patient sought medical advice, and a large firm abdominal mass, situated in the upper midabdomen, slightly to the left of the umbilicus was discovered upon examination. It was well-defined, movable, and suggested a pedunculated fibroid sarcoma or mesentery tumor. There was no bleeding and no rectal symptoms were complained of by the patient. Constipation was not a factor. The patient had developed a limp in the right leg during the past 6 months. A progressive paralysis of the right leg developed with Babinski, clonus and bilateral exaggeration of the knee jerks; sensory impairment for pain and temperature over the body was discovered as high as the nipple line. The patient was not aware of this change until disclosed at examination. The roentgen ray studies of the chest and spine were negative for metastasis.

The internist made a diagnosis of spinal cord tumor in the upper thoracic region and felt the spinal region should

be operated on before the abdominal tumor. I removed a flattened endothelioma, non-malignant, 4 cm. in length, situated extra-durally on the right side of the cord, extending from the third to the seventh dorsal vertebrae. The abdominal tumor still awaits exposure and identification next week.

Here is a situation where abdominal surgery might easily have been justified, but the fine clinical judgment of the internist demanded that the signs of cord pressure be removed, first, as the abdominal mass could await its appropriate term.

It seems to me that we may all feel proud of such diagnostic acumen based upon an understanding of certain fundamental neurological manifestations. I concur with Dr.

Kiefer in his timely admonitions and appreciate the privilege of discussing this paper.

DR. EVERETT D. KIEFER (Closing the discussion): I have little more to add.

Dr. Fay should be the one to answer Dr. Shattuck's question, but to me laminectomy is a fairly serious operation and one would not explore for arachnoiditis without having some fairly definite neurological signs, or fairly definite evidence of changes in the spinal fluid, or in the case I just mentioned, where one had exhausted every other means of giving relief to the patient. This patient was rapidly becoming a morphine addict and he was explored perhaps on a little less evidence than one would usually want.

## ABSTRACTS

BLOOMFIELD, ARTHUR L.

*Early Cancerous Changes in Peptic Ulcer. J. A. M. A., 104:1197, April 6, 1935.*

The author considers the subject to benign ulcer and its relationship of malignancy of the stomach.

He reviews the criteria for the early diagnosis of carcinomatous gastric ulcer. The roentgen examination is not always conclusive. The assumption that benign ulcer has a long history and cancer a short history cannot always be relied upon. Consideration of age and sex are of little help. The size of the gastric ulcer is generally helpful in the differentiation, but there are many exceptions to this rule. The presence of gastric secretion or absence of it when carefully analyzed is not of much help since cancer may arise in a stomach with an acidity and a chronic gastritis on the one hand and on the other arising from a previous benign ulcer with little change in gastric secretion. Response to a medical regime of the ulcer cannot be used as conclusive evidence either for or against malignancy, because a malignant ulcer may respond to medical treatment and benign ulcers may not.

Prophylactic surgery carries with it definite risk.

The author therefore concludes that patients with benign ulcers should be treated as such until weighty evidence

accumulates to change that impression, realizing that a number of malignancies will be thus overlooked in their incipency.

Francis D. Murphy, Milwaukee.

SAPOZNIK, H. J.; ARENS, R. A.; MEYER, JACOB, AND NECHLES, HEINRICH.

*The Effect of Oil of Peppermint on the Emptying Time of the Stomach. J. A. M. A., 104:1792, May 18, 1935.*

The Authors have previously reported that oil of peppermint diminished gastric acidity. In this study they report the effect of oil of peppermint on the emptying time of the stomach. In the empty stomach small doses of oil of peppermint had no effect on the hunger contractions of dog or man. Large quantities of oil of peppermint decreased the motility in six tests and produced no change in two.

In experiments with a meat meal and oil of peppermint, shortening of the emptying time was observed.

In six normal young females the addition of two c.c. of oil of peppermint to a barium-milk shortened the emptying time of the stomach as observed fluoroscopically.

These studies seem to explain the popular use of oil of peppermint in many stomach remedies. The use of peppermint candy and peppermint alcohol after a heavy meal appears useful because by increasing motility distension and fullness are relieved more promptly.

Francis D. Murphy, Milwaukee.

## SECTION II—*Experimental Physiology*

### The Autoregulation of the Gastric Secretion\*

By

J. J. DAY, M.D.

and

D. R. WEBSTER, M.D., Ph.D.

MONTREAL, CANADA

THE problem of the autoregulation of the gastric secretion may be considered under two headings. It may be discussed from the point of view of (1) the influence which the gastric juice accumulating in the stomach or the duodenum may have on the secretory activity of the gastric glands, or (2) the changes in the composition of the gastric juice which may occur in the same circumstances, or in other words the quantitative or qualitative changes in the gastric juice due to its own presence in the stomach or duodenum. These two aspects should be carefully differentiated, as in this field recently some of the workers have been considering the quantitative aspect and others the qualitative, and this has led to some confusion.

More than thirty years ago, Sokolov (1904), working in Pavlov's Laboratory on dogs with a gastric and a duodenal fistula, Pavlov pouch and the stomach disconnected from the duodenum, established that the introduction of 0.5 per cent hydrochloric acid into the stomach caused a marked inhibition of the secretion from the pouch; on the other hand, lactic and butyric acid stimulated the secretion. It was also noted that the introduction of meat and water into the main stomach caused the pouch to secrete, but the secretion was small and in four to five hours had practically ceased. Analysis of this phenomenon showed that the inhibition of the pouch secretion was due neither to the increased pressure on the walls of the main stomach resulting from increase of the gastric contents, nor to stimulation caused by absorption of the products of meat digestion, but to the rising concentration of hydrochloric acid in the stomach. Inhibition of the secretory activity of the pouch was also noted when gastric juice was introduced into the duodenum. Unfortunately very few experiments of this kind were performed. A few years before in the same laboratory Shemiakin (1901) found that, when hydrochloric acid in physiological concentrations was introduced into the duodenum, it inhibited the secretion of the pyloric glands, but that when applied locally it stimulated the secretion of these glands. Pavlov and his pupils, in discussing the autoregulation of the gastric secretion, were considering not one particular constituent of the gastric juice, namely acid, but the gastric juice *in toto* (cf. Babkin, 1928).\*

The idea that the secretion of hydrochloric acid varies under certain circumstances was originated by Rosemann (1907, 1920). His theory created a great controversy, and a voluminous literature arose on the question of the mechanism of the secretion of hydrochloric acid by the gastric glands. It was opposed to Pavlov's theory of the constancy of the acidity of the secretion produced by the gastric glands.

We have no intention of discussing the corresponding literature but shall merely mention a few papers which have direct relation to our problem. The most ardent supporters of Rosemann are MacLean and his co-workers (1928), who developed his theory to the extreme. Whereas Rosemann speaks only of slight variation in the distribution of the chloride between the hydrochloric acid and the chlorides of the gastric juice, MacLean, Griffiths and Williams (1928) believe that at the end of the secretory period the secretion of acid in the stomach of the dog is replaced by a secretion of neutral fluid containing chloride, which reduces the acidity to the fasting level. As was demonstrated by one of us (Webster, 1929), under normal conditions the gastric glands of the dog never secrete sufficient neutral fluid to dilute the gastric contents and reduce their acidity. One of the factors which play an important part in the neutralization of gastric acidity at the end of the secretory period, when the volume of the secretion is greatly diminished, is the alkaline gastric mucus. Bolton and Goodhart (1931 and 1933) came to analogous conclusions.

Further, MacLean and Griffiths (1928 b) came to the conclusion that the concentration of hydrochloric acid in the normal human stomach is regulated automatically by the hydrogen ion concentration of the gastric juice. According to them, a certain concentration of acid in the stomach inhibits the secretion of acid. The secretion of the latter is replaced by the secretion of a fluid containing neutral chlorides, which reduces the acidity of the gastric contents by diluting them.

\*The cause of the confusion of these two different concepts (secretion of gastric juice and secretion of acid) probably originated in an unfortunate English rendering of the corresponding text in I. P. Pavlov's book on "The Work of the Digestive Glands," translated by W. H. Thompson (2nd ed., London, 1910, p. 115). The part where Pavlov refers to the gastric juice reads as follows: "With the same dogs we also discovered a new form of autoregulation on the part of the stomach, which concerns the secretion of hydrochloric acid. It appears that the acid prevents the further secretion of gastric juice when it has accumulated in any considerable quantity within the cavity of the organ."

\*From the Department of Physiology, McGill University, Montreal. Submitted July 2, 1935.

In a series of recent publications Wilhelmj *et al.* (1933, 1934 a and b) arrived at a diametrically opposite conclusion to that of MacLean and his co-workers. They found that solutions of hydrochloric acid of 0.024 to 0.173 N, introduced into a Heidenhain pouch or into the whole intact stomach of a dog, did not inhibit the secretion of acid. The secretion of the gastric juice was activated by means of histamine. This conclusion was reached indirectly by estimating the different inorganic compounds of the mixed fluid aspirated from the stomach cavity or pouch. Neither from MacLean's nor from Wilhelmj's experiments can any conclusions be drawn concerning the volume of the gastric secretion.

The importance of the problem of the autoregulation of the gastric secretion led us to reinvestigate this question. We were in an especially favorable position to study the effect produced on the gastric secretion by the introduction of acid solutions into the duodenum, since we had at our disposal several dogs with oesophagotomy, gastric and duodenal metal fistulae, and the stomach completely disconnected from the duodenum at the pyloro-duodenal junction. This was the more important since Sokolov only performed a very limited number of experiments of this kind. The problem of the autoregulation of the flow of gastric juice was investigated experimentally in the present study, without regard to the changes in its acidity.

#### METHODS

Two dogs ("F" and "L") with oesophagotomy, gastric and duodenal fistulae, and the stomach disconnected from the duodenum, were employed in this investigation. Some experiments were also done on a dog ("T") with a Heidenhain pouch and gastric fistula. The obstructed animals were fed in the usual manner with the food-mixture described by Scott and Ivy (1931), which was introduced into the duodenum through the duodenal fistula (see Webster and Armour, 1932 a). According to the plan of each separate experiment the food-mixture was or was not introduced. In certain experiments solutions of gastric juice of known acidity were introduced into the duodenum through the duodenal fistula. The free acidity of the gastric juice collected during the experiments was determined by titration with 1.50 N sodium hydroxide, with Töpfer's reagent as indicator; the total acidity was estimated in the same way with phenolphthalein as indicator.

#### EXPERIMENTAL RESULTS

In animals such as Dogs "F" and "L", prepared in the manner described above, there is always a long latent period between the time of the introduction of food into the intestine and the resulting gastric secretion. Once the secretion starts, it becomes gradually more and more copious until it reaches a certain point, after which it gradually declines. The whole period of gastric secretion lasts about 12 to 15 hours. If the food-mixture is not introduced into the duodenum, there is hardly any secretion of gastric juice (Webster and Armour, 1932 a). This is a convincing demonstration of the stimulating effect exerted by food substances and the products of their digestion on the gastric glands from the intestine, a phenomenon known as the "intestinal phase of gastric secretion" (see Babkin, 1928, p. 272).

In view of these facts the question naturally arose as to why, in unobstructed dogs with a stomach pouch or with a simple gastric fistula, the influence of the "intestinal phase" of gastric secretion was not more obvious instead of being practically absent. It is a

well recognized fact that in these animals, shortly after the food has left the stomach, the secretion ceases. If the latent period of action of the secretory substances in the intestine lasts several hours, and the secretagogue effect on the gastric glands is manifested for a greater number of hours after that, as observed in our obstructed animals, one would expect the secretion resulting from the chyme leaving the stomach and entering the intestine to continue for a noticeable period. The daily observations in our laboratory show that this is not the case.

Table I shows the results of an experiment on a dog with a Heidenhain pouch and gastric fistula, in which there is little evidence of any intestinal stimulation

TABLE I

Dog "T".—Heidenhain pouch and gastric fistula

|             |                                                                                                                                                                        |
|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 11:00 a. m. | Dog fed usual daily meal of meat and porridge.                                                                                                                         |
| 4:00 p. m.  | Total secretion from pouch, 70 c.c. Gastric fistula opened; some food remains washed out.                                                                              |
| 5:00 p. m.  | Secretion from pouch during one hour, 1.5 c.c. of acid gastric juice.                                                                                                  |
| 6:00 p. m.  | Secretion from pouch, 0.1 c.c.                                                                                                                                         |
| 7:00 p. m.  | No secretion from pouch; reaction in pouch alkaline to litmus.                                                                                                         |
| 8:00 p. m.  | No secretion from pouch; reaction alkaline. Gastric fistula opened; slight food residue. Mucous membrane of stomach acid. Fistula left open.                           |
| 9:00 p. m.  | No secretion from pouch; reaction of its mucous membrane alkaline. Stomach secreted during one hour 2.1 c.c. of acid gastric juice containing mucus. Experiment ended. |

after the stomach has been emptied. The very slight acid secretion of the stomach might easily be due either to food particles clinging to the fold of the mucous membrane or to some conditioned gastric reflexes. The pouch, however, where any true hormonal effect would be obtained, remained alkaline.

It was apparent that the main difference in obstructed as compared with non-obstructed animals is the prevention of the passage of the gastric secretion from the stomach to the duodenum and the absence of peptic digestion. Several types of experiment were performed to verify the suggestion that the acid of the gastric juice might act as an inhibitory agent on the gastric secretion.

Table II shows the results of sham-feeding in two experiments carried out on a dog with oesophagotomy, gastric and duodenal fistulae, and the stomach obstructed at the pylorus. The Experiment of May 1 is a control sham-feeding experiment. In the Experiment of May 17, 50 c.c. of gastric juice diluted with an equal quantity of water (approximate acidity, 0.25 per cent hydrochloric acid) were introduced into the duodenum before the sham-feeding was commenced. The introduction of gastric juice into the duodenum, as a preliminary to sham-feeding, depressed the secretory effect of the sham-feeding (in the first two ten-minute periods 9.0 c.c. and 13.5 c.c. were obtained, as against 16.5 c.c. and 19.0 c.c. in the control experiment). But the inhibition of the gastric secretion was especially striking when the gastric juice was introduced into the duodenum while the gastric glands were actually secreting. The total volume of the secretion during one hour fell from 47.7 c.c. to 27.3 c.c. The preliminary introduction of twice as large an amount of water into

the duodenum of the same dog did not produce any inhibition, as may be seen from the following figures:

*Dog "F".—Exp. May 11*

| Time<br>a. m. | Volume of<br>Gastric<br>Secretion<br>c.c. |
|---------------|-------------------------------------------|
| 9:00-9:30     | 1.5                                       |
| 9:30-10:00    | 0.0                                       |
| 10:00-10:30   | 3.0                                       |
| 10:30-10:40   | 9.7                                       |
| 10:40-10:50   | 19.0                                      |
| 10:50-11:00   | 15.5                                      |
| 11:00-11:10   | 6.0                                       |
| 11:10-11:20   | 3.0                                       |
| 11:20-11:30   | 2.1                                       |

Total for one hour: 55.3

Between 10 and 10:30, 100 c.c. of water introduced into duodenum.

Between 10:30 and 10:40 dog sham-fed.

fell, but the absolute figures for the combined acidity did not deviate very much from those of the other samples (except Sample 4). This shows that the neutralizing factors (mucus, pyloric juice, etc.) remained constant during almost the whole of the experiment.

Another proof that acid, when introduced into the duodenum, is the chief factor in inhibiting the gastric secretion is seen in an experiment in which neutralized gastric juice was introduced into the intestine. Table IV shows the results of two experiments on Dog "L", which was prepared in the same way as Dog "F". During the period in which these experiments were performed, the gastric glands of Dog "L" were in a state of hypersecretion. As described by Webster and Armour (1932 b), this state of hypersecretion depends chiefly on the disturbance of the balance between the substances lost with the gastric juice and those introduced into the body. Therefore this type of secretion

TABLE II

*Dog "F".—Oesophagotomy, gastric and duodenal metal fistulae, and obstruction at the pylorus*

| Exp. May 1 (control) |                   |                         |              | Exp. May 17  |                   |                         |              |
|----------------------|-------------------|-------------------------|--------------|--------------|-------------------|-------------------------|--------------|
| Time<br>min.         | Gastric Secretion |                         |              | Time<br>min. | Gastric Secretion |                         |              |
|                      | Vol.<br>c.c.      | Free<br>HCl<br>m.eq./l. | Total<br>HCl |              | Vol.<br>c.c.      | Free<br>HCl<br>m.eq./l. | Total<br>HCl |
| 30                   | mucus             | —                       | —            | 30           | 1.5               | —                       | —            |
| 10                   | 16.5              | 60                      | 81           | 15           | 0.8               | —                       | —            |
| 10                   | 19.0              | 128                     | 145          | 10           | 9.0               | 96                      | 115          |
| 10                   | 5.5               | 136                     | 155          | 10           | 13.5              | 131                     | 152          |
| 10                   | 2.5               | 117                     | 139          | 10           | 4.0               | 145                     | 160          |
| 10                   | 2.5               | 115                     | 136          | 10           | 0.2               | —                       | —            |
| 10                   | 1.7               | 117                     | 147          | 10           | 0.5               | —                       | —            |
|                      |                   |                         |              | 10           | 0.0               | —                       | —            |
| Total: 47.7          |                   |                         |              | Total: 27.3  |                   |                         |              |

That the acid is the chief agent in the gastric juice which produces the inhibition is shown in the following experiments. Table III represents an experiment during which the secretion produced by sham-feeding with meat in an obstructed dog was definitely inhibited by the introduction into the duodenum of a 0.25 per

differs greatly from that activated by sham-feeding. Nevertheless the introduction of 100 c.c. of pure gastric juice into the duodenum almost completely inhibited the spontaneous secretion for one hour (see Experiment March 11). When neutralized gastric juice was introduced into the duodenum, only a weak

TABLE III

*Dog "F".—Oesophagotomy, gastric and duodenal metal fistulae, and obstruction at the pylorus*

| Exp. June 21 |              |                   |                         |              |                       |
|--------------|--------------|-------------------|-------------------------|--------------|-----------------------|
| Sample       | Time<br>min. | Gastric Secretion |                         |              |                       |
|              |              | Vol.<br>c.c.      | Free<br>HCl<br>m.eq./l. | Total<br>HCl | Com-<br>bined<br>acid |
| 1            | 60           | 13.0              | 100                     | 127          | 27                    |
| 2            | 15           | 1.8               | 90                      | 124          | 34                    |
| 3            | 10           | 10.0              | 101                     | 134          | 33                    |
| 4            | 10           | 14.25             | 130                     | 141          | 11                    |
| 5            | 10           | —                 | —                       | —            | —                     |
| 6            | 10           | 2.0               | 85                      | 113          | 28                    |
| 7            | 10           | 2.2               | 86                      | 121          | 35                    |
| 8            | 10           | 5.5               | 106                     | 143          | 37                    |
| 9            | 10           | 10.8              | 114                     | 145          | 31                    |
| 10           | 10           | 7.6               | 121                     | 153          | 32                    |

cent solution of hydrochloric acid. On the day of this experiment, the dog had a greater fasting secretion than usual, which again appeared when the effect of the acid had passed off. As usual with diminution of the secretion the total and free acidities of the juice

temporary inhibition could be observed (Experiment Feb. 6).

In the next set of experiments on Dog "F", of which two are represented in Table V, the gastric secretion was stimulated by the procedure of feeding. Scott and

Ivy's diet was introduced through the duodenal fistula in amounts of 80 c.c. every 15 minutes. As usual the secretion did not commence till after a long latent period. In the experiment of July 27, the feeding of the food-mixture was replaced at 3 p. m. by feeding 40 c.c. of the food-mixture combined with 40 c.c. of pure gastric juice (free acidity, 0.347 per cent hydrochloric acid; total acidity, 0.474 per cent hydrochloric

mately 0.12 per cent hydrochloric acid. 60 c.c. of food mixture and 20 c.c. of gastric juice (free acidity of undiluted juice, 0.31 per cent hydrochloric acid; total acidity, 0.49 per cent hydrochloric acid) were introduced, as in the previous experiment, at 15-minute intervals in four feedings. As may be seen from the figures of this experiment, the gastric secretion was again greatly inhibited, only 0.95 e.c. of juice being

TABLE IV

*Dog "L".—Oesophagotomy, gastric and duodenal metal fistulae, and obstruction at the pylorus. The gastric glands were in a state of hypersecretion. Both experiments begun at 9 a. m.*

| Exp. March 11 |           |                                |                                                     | Exp. Feb. 6 |           |                                |                                                                 |
|---------------|-----------|--------------------------------|-----------------------------------------------------|-------------|-----------|--------------------------------|-----------------------------------------------------------------|
| Sample        | Time min. | Vol. of gastric secretion c.c. | Remarks                                             | Sample      | Time min. | Vol. of gastric secretion c.c. | Remarks                                                         |
| 1             | 15        | 31.0                           | 100 c.c. of gastric juice introduced into duodenum. | 1           | 30        | 20.0                           | 100 c.c. of neutralized gastric juice introduced into duodenum. |
| 2             | 15        | 24.0                           |                                                     | 2           | 30        | 23.0                           |                                                                 |
| 3             | 15        | 29.0                           |                                                     | 3           | 30        | 16.0                           |                                                                 |
| 4             | 15        | 7.0                            |                                                     | 4           | 30        | 22.0                           |                                                                 |
| 5             | 15        | 0.3                            |                                                     |             |           |                                |                                                                 |
| 6             | 15        | 2.0                            |                                                     |             |           |                                |                                                                 |
| 7             | 15        | 16.0                           |                                                     |             |           |                                |                                                                 |
| 8             | 15        | 29.0                           |                                                     |             |           |                                |                                                                 |

acid). The total volume of fluid introduced into the intestine remained the same, i.e. 80 e.c. This combination of the mixture and gastric juice was again given at 3:15, 3:30 and 3:45 p. m. At 4 p. m. the regular feeding was resumed. In this experiment therefore hydrochloric acid in a solution of approximately 0.25 per cent (probably less owing to the neutralizing effect of the food mixture) was introduced into the duo-

secreted in the last hour. The results of this experiment are the more striking inasmuch as the concentration of acid in the mixture introduced into the intestine was very low and certainly did not exceed that of the duodenal chyme under normal conditions.

### CONCLUSIONS

The experiments here reported demonstrate that the gastric secretion, stimulated through the parasympa-

TABLE V

*Dog "F".—Oesophagotomy, gastric and duodenal metal fistulae, and obstruction at the pylorus. Effect of feeding with Scott and Ivy's food-mixture and with this food-mixture to which gastric juice has been added, 80 c.c. being introduced in each case into the duodenum every 15 minutes*

| Exp. July 27 |                        |                   |                   |           | Exp. Aug. 3                                                                                                                                                                                      |        |                        |                   |                   |           |                                                                                                                                                                                                 |
|--------------|------------------------|-------------------|-------------------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|------------------------|-------------------|-------------------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sample       | Time                   | Gastric Secretion |                   |           | Remarks                                                                                                                                                                                          | Sample | Time                   | Gastric Secretion |                   |           | Remarks                                                                                                                                                                                         |
|              |                        | Vol. c.c.         | Free HCl m.eq./l. | Total HCl |                                                                                                                                                                                                  |        |                        | Vol. c.c.         | Free HCl m.eq./l. | Total HCl |                                                                                                                                                                                                 |
| 1            | 9:00 a.m. -10:00 a.m.  | 2.0               | 77                | 128       | 9 a.m., feed-<br>ing begun.                                                                                                                                                                      | 1      | 9:00 a.m. -10:00 a.m.  | 0.0               | —                 | —         | 0 n.m., feed-<br>ing begun.                                                                                                                                                                     |
| 2            | 10:00 a.m. -11:00 a.m. | 1.3               | —                 | —         |                                                                                                                                                                                                  | 2      | 10:00 a.m. -11:00 a.m. | 5.5               | 50                | 90        |                                                                                                                                                                                                 |
| 3            | 11:00 a.m. -12:00 noon | 7.0               | 61                | 100       |                                                                                                                                                                                                  | 3      | 11:00 a.m. -12:00 noon | 10.1              | 10                | 55        |                                                                                                                                                                                                 |
| 4            | 12:00 noon- 1:00 p.m.  | 11.0              | 94                | 139       |                                                                                                                                                                                                  | 4      | 12:00 noon- 1:00 p.m.  | 17.0              | 40                | 85        |                                                                                                                                                                                                 |
| 5            | 1:00 p.m. - 2:00 p.m.  | 14.0              | 92                | 125       | 3 p.m., 40<br>c.c. of food-<br>mixture<br>given with<br>40 c.c. of<br>gastric<br>juice; this<br>repeated nt<br>3:15, 3:30<br>and 3:45<br>p.m.<br>4-6:30 p.m.,<br>regular<br>feedings<br>resumed. | 5      | 1:00 p.m. - 2:00 p.m.  | 15.0              | 79                | 117       | 3 p.m., 60<br>c.c. of food<br>mixture<br>given with<br>20 c.c. of<br>gastric<br>juice; this<br>repeated nt<br>15 min. in-<br>tervals for<br>8 feedings.<br>Last feed-<br>ing given<br>4:45 p.m. |
| 6            | 2:00 p.m. - 3:00 p.m.  | 10.0              | 110               | 125       |                                                                                                                                                                                                  | 6      | 2:00 p.m. - 3:00 p.m.  | 5.0               | 37                | 78        |                                                                                                                                                                                                 |
| 7            | 3:00 p.m. - 3:30 p.m.  | 1.5               | 99                | 134       |                                                                                                                                                                                                  | 7      | 3:00 p.m. - 3:30 p.m.  | 4.8               | 65                | 109       |                                                                                                                                                                                                 |
| 8            | 3:30 p.m. - 4:00 p.m.  | 0.0               | —                 | —         |                                                                                                                                                                                                  | 8      | 3:30 p.m. - 4:00 p.m.  | 1.5               | —                 | —         |                                                                                                                                                                                                 |
| 9            | 4:00 p.m. - 4:30 p.m.  | 0.6               | —                 | —         |                                                                                                                                                                                                  | 9      | 4:00 p.m. - 4:30 p.m.  | 3.1               | 18                | 90        |                                                                                                                                                                                                 |
| 10           | 4:30 p.m. - 5:00 p.m.  | 1.2               | —                 | —         |                                                                                                                                                                                                  | 10     | 4:30 p.m. - 5:00 p.m.  | 0.75              | —                 | —         |                                                                                                                                                                                                 |
| 11           | 5:00 p.m. - 5:30 p.m.  | 1.0               | —                 | —         |                                                                                                                                                                                                  | 11     | 5:00 p.m. - 5:30 p.m.  | 0.2               | —                 | —         |                                                                                                                                                                                                 |
| 12           | 5:30 p.m. - 6:10 p.m.  | 25.0              | 94                | 125       |                                                                                                                                                                                                  | 12     | 5:30 p.m. - 6:30 p.m.  | 70.0              | 58                | 100       |                                                                                                                                                                                                 |

denum. As a result the gastric secretion was almost completely stopped for two hours.

In order to approach still nearer to the normal conditions of digestion, in which chyme of an approximate acidity of 0.15 per cent hydrochloric acid passes from the stomach into the duodenum, in the Experiment of August 3 the concentration of the gastric juice added to the food mixture was lowered to approxi-

thetic nervous system or by the presence in the intestine of food substances and the products of their disintegration, is inhibited by the introduction of hydrochloric acid into the duodenum. The same phenomenon was noted when the gastric glands of one of the animals was in a state of hypersecretion. Therefore it may be safely concluded from this investigation that, in all cases where the gastric glands are stimulated to



secrete gastric juice by natural means, the presence of acid in the duodenum and upper small intestine markedly restricts their secretory activity. This fact alone is sufficient to explain why in normal animals, in which the passage of the acid chyme from the stomach to the intestine is not restricted, the "intestinal phase" of the gastric secretion is practically absent. The effect which the introduction of hydrochloric acid into the duodenum might have on the gastric secretion provoked by drugs, e.g. histamine and pilocarpine, was not investigated by us, but this is now being studied in our laboratory.

The mechanism of the inhibitory action of hydrochloric acid on the gastric secretion is not quite clear. Facts are accumulating which show that a substance inhibiting both the gastric secretion and motility may be extracted from the intestinal mucosa (the "Entero-gastrone" of Kosaka, Lim, Ling and Liu (1932), Lim (1933), Lim, Ling and Liu (1934), Ivy (1935); the "Biodialysate" of Walawski (1930)). Therefore it is very probable that a *chalone* inhibiting the gastric secretion may be formed in the intestinal mucosa when such substances as fat or hydrochloric acid come in contact with the intestinal mucosa. However, the possibility cannot be excluded that the inhibition may be due in part to nervous impulses arising in the intestine, e.g. from distension with fluid, and by reflex action arresting the activity of the gastric glands. The relations in respect of gastric secretion may be analogous to those which Quigley, Zettelman and Ivy (1934) found for the motility of the stomach, namely, that the inhibitory process evoked by fat involves both nervous and humoral mechanisms. Undoubtedly the effect of the acid, as such, is the chief factor de-

termining the inhibition of the gastric secretion. However, in some of our experiments (*cf.* Table IV) the introduction of neutral fluid into the duodenum in considerable amounts somewhat inhibited the flow of gastric juice. In such cases we are probably dealing with a reflex inhibition of the gastric secretion provoked by distension of the intestine, but in the majority of the experiments the factor of distension was carefully avoided by giving only amounts which we knew from experience in feeding the dogs would not cause the slightest distension. Further experiments are now being done with the object of clearing up this point and also of determining whether this inhibitory effect is peculiar to the acids of the gastric juice or whether it may be provoked by other acids or chemicals.

### SUMMARY

Introduction into the duodenum of 0.25 per cent hydrochloric acid or of gastric juice, diluted two to four times, inhibits the gastric secretion stimulated (a) through the parasympathetic nervous system or (b) by the presence in the intestine of food substances or the products of their digestion. The same effect was produced by the acid in some cases of hypersecretory activity of the gastric glands. The theory is advanced that the passage of the acid chyme from the stomach into the duodenum causes the gastric secretion to diminish, this being an important factor in regulating the activity of the gastric glands.

### ACKNOWLEDGEMENT

This work was carried out under the direction of Dr. B. P. Babkin, to whom we are indebted for much helpful advice and criticism.

### REFERENCES

- Babkin, B. P.: *Die äussere Sekretion der Verdauungsdrüsen*. 2nd ed., Berlin, 1928, p. 274 ff., 424 ff.  
 Bolton, C., and G. W. Goodhart: *Jour. Physiol.*, 73:115, 1931.  
 Bolton, C., and G. W. Goodhart: *Jour. Physiol.*, 77:287, 1933.  
 Ivy, A. C.: *Amer. Jour. Dig. Dis. and Nutr.*, 2:58, 1935.  
 Kosaka, T.; R. K. S. Lim; S. M. Ling, and A. C. Liu: *Chin. Jour. Physiol.*, 6:107, 1932.  
 Lim, R. K. S.: *Quart. Jour. Exp. Physiol.*, 23:264, 1933.  
 Lim, R. K. S.; S. M. Ling, and A. C. Liu: *Chin. Jour. Physiol.*, 8:219, 1934.  
 MacLean, H., and W. J. Griffiths: *Jour. Physiol.*, 65:63, 1928 (a).  
 MacLean, H., and W. J. Griffiths: *Jour. Physiol.*, 66:356, 1928 (b).  
 MacLean, H.; W. J. Griffiths, and B. W. Williams: *Jour. Physiol.*, 65:77, 1928.  
 Quigley, J. P.; H. J. Zettelman, and A. C. Ivy: *Am. Jour. Physiol.*, 105:643, 1934.  
 Rosemann, R.: *Pflüger's Arch.*, 118:467, 1907.  
 Rosemann, R.: *Virchow's Arch.*, 229:67, 1920-21.  
 Scott, H. G., and A. C. Ivy: *Annals Surg.*, June: 1197, 1931.  
 Shemiakin, A. I.: Thesis, St. Petersburg, 1901.  
 Sokolov, A.: Thesis, St. Petersburg, 1904.  
 Walawski, J.: *Medyc. Doswiadc. i społeczna*, 11:348, 1930. (Abstract in French.)  
 Webster, D. R.: *Amer. Jour. Physiol.*, 90:718, 1929.  
 Webster, D. R., and J. C. Armour: *Trans. Roy. Soc. Canada*, 26, Section V: 109, 1932 (a).  
 Webster, D. R., and J. C. Armour: *Canad. Med. Assoc. Jour.*, 27:240, 1932 (b).  
 Wilhelmj, C. M.; L. C. Heinrich, and F. C. Hill: *Proc. Soc. Exp. Biol. and Med.*, 31:969, 1934.  
 Wilhelmj, C. M.; I. Neigus, and F. C. Hill: *Amer. Jour. Physiol.*, 106:381, 1933.  
 Wilhelmj, C. M.; I. Neigus, and F. C. Hill: *Amer. Jour. Physiol.*, 107:490, 1934 (a).  
 Wilhelmj, C. M.; I. Neigus, and F. C. Hill: *Amer. Jour. Physiol.*, 108:197, 1934 (b).

## ABSTRACTS

HILL, F. C.; HENRICH, L. C., AND WILHELMJ, C. M.

*The Mechanism by Which the Acidity of an Acid Meal is Reduced in the Stomach.* S., G. and O., Vol. 60, No. 5, May, 1935, pp. 966-968.

The authors performed experiments to determine the exact mechanism of neutralization of an acid meal in the stomach. That dilution by regurgitation of duodenal contents, and by the secretion of mucus, occurs, is an accepted fact. To what extent the reduction of acidity in the stomach is due to the alkalinity of duodenal contents, and to what extent it is due to dilution, has not been determined.

The authors using a stock solution of approximately

tenth normal hydrochloric acid containing a small quantity of phenolsulphonphthalein experimented on healthy dogs. The test meal consisted of 300 cc. of the stock solution. Samples of this meal were withdrawn every fifteen minutes for an hour, or as long as any fluid could be obtained. By colorimetric tests the amount of dilution of the meal was determined. Chemical analyses of the samples for neutral chlorides, and total chlorides, showed the extent of neutralization.

By that method the authors found that an average of 65 per cent of the reduction was due to dilution, and 35 per cent to neutralization.

Nelson M. Percy, Chicago.

## SECTION III—Nutrition

### Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes

#### IV. Block of the Reticulo-Endothelial System with Special Reference to the Kupffer Cell\*

By

T. L. ALTHAUSEN, M.D.

and

B. E. BLOMQUIST, M.A.

with technical assistance of

E. F. WHEDON, M.S.

SAN FRANCISCO, CALIFORNIA

NUMEROUS investigators have established the fact that the reticulo-endothelial system plays a part in the metabolism of fats and proteins. Comparatively little work has been done regarding the participation of this system in the metabolism of carbohydrates in spite of the fact that our knowledge regarding the fate of carbohydrates in the body is more advanced than that of other food elements.

Several workers have studied the effect of reticulo-endothelial block on the blood-sugar level, but their results have been conflicting (1). Klein and Levinson (2), during continuous intravenous injections of India ink, observed an initial rise in blood-sugar, followed by a prolonged fall which they ascribed to exhaustion of available glycogen. Nakaya (3), from a study of hepatic glycogen after carbohydrate feedings before and after intravenous injection of India ink, concluded that the formation of glycogen is due largely to activity of the reticulo-endothelial system. Messina (4) performed extensive experiments showing reduced dextrose tolerance and decreased hyperglycemia after epinephrine in blocked rabbits. Unfortunately, the use of toxic blocking substances which caused marked loss of weight and eventually death in all animals rendered the significance of his data uncertain, especially since these findings are similar to those obtained by one of us (T.L.A.) after poisoning of the liver with phosphorus and with chloroform (5, 6).

Our investigation consisted of first depressing the function of the intravascular components of the reticulo-endothelial system by partial block, and then studying the blood-sugar level, the responses of the organism to "loads" imposed on the mechanisms deal-

ing with assimilation and with mobilization of sugar, and the glycogen content of the liver and muscles.

#### METHODS

In blocking experiments, probably more than in any other biological research, the evaluation of the obtained data depends upon the readers' exact knowledge of the experimental conditions.

*Animals.* Jaffé (7) recommends rabbits as being among the animals most suited to blocking experiments. Accordingly healthy, growing rabbits weighing about 2 kg. were used in this work. They were kept on a diet consisting of rolled oats and alfalfa hay, with the addition of green cabbage leaves and carrots twice a week.

*Blocking substances.* Since our object was to produce physical block of the reticulo-endothelial system limited to its intravascular elements, the blocking substance of choice was a coarse, non-toxic, chemically inert, dispersed colloid which would not pass through endothelial walls, thus avoiding block of extravascular reticulo-endothelial cells or penetration into parenchymatous cells of glandular organs. During the early part of our work we used one part of Higgins' Black American India Ink diluted with two parts of distilled water as a substance thought to answer these requirements (8, 9). Later an article by Victor, Van Buren and Smith (10), dealing with the influence of India ink injections on the hepatic excretion of dyes, brought to our attention the fact that India ink may contain some toxic element, possibly camphor. Higgins Company refused our request to name the ingredients of their product, and therefore we repeated our experiments using separately the precipitated carbon and the carbon-free fractions of India ink, prepared according to directions received from Doctor H. P. Smith. Since eight rabbits injected with the resuspended carbon died from embolism following one or two injections, we substituted for carbon a suspension of colloidal graphite\* in gum acacia. In preparation, the directions of Higgins and Murphy (11) were followed.

In attempting to reduce the functional capacity of the reticulo-endothelial system, the so-called Arndt-Schulze law must be taken into consideration. This repeatedly confirmed law postulates that small amounts of a blocking

\*From the Department of Medicine and the George Williams Hooper Foundation of the University of California Medical School, San Francisco. Assisted by a grant from the Christine Brown Fund for Medical Research.

†Presented before the 55th Annual Session of The American Gastroenterological Association, Atlantic City, N. J., June 16, 1935.

Approved by the Publications' Committee of the Association.

\*Hydram-Kollag "300" of E. de Haen Co.

substance stimulate, and large amounts depress, the function of the storing cells. Frequently errors are committed by giving an insufficient dose. From at least one study (12), thus far unconfirmed, it appears possible that an

Average Increase of Sugar in Mg.

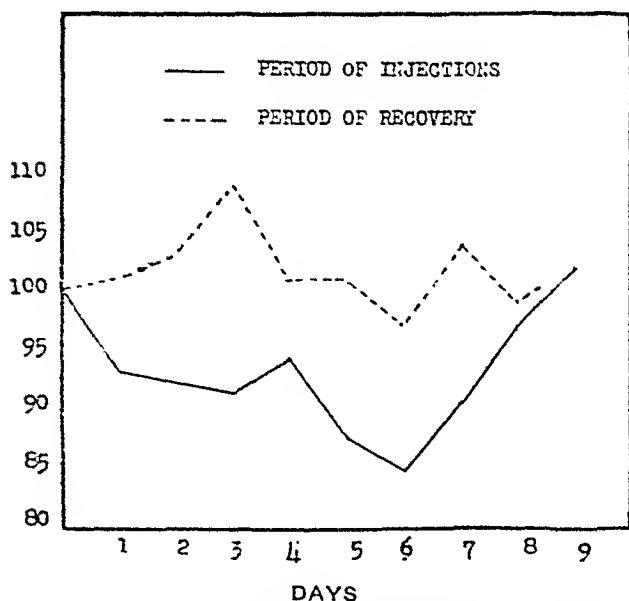


Chart I. Morning blood sugar of 12 rabbits during and of 6 rabbits after a period of daily India ink injections (5 c.c. given 16 hours previously).

overdose may also increase the functional capacity of the reticulo-endothelium. We attempted to avoid both extremes by determining the effect of different amounts of the blocking substance.

**Timing of experiments.** Opinions differ as to the duration of effective block produced by single injections of a blocking substance. According to some authors (13), the effect of multiple injections may last as long as several weeks; others deny the existence of any cumulative effect with prolonged vital staining (7). In view of such disagreement, and because it is possible that different functions of the reticulo-endothelial system may manifest impairment for different periods of time, we tested our rabbits in separate experiments at intervals of 30 minutes, 5 hours, 16 hours and 24 hours following injection of the blocking substance.

**Tests.** In addition to single blood-sugar determinations, two procedures were employed: 1. The dextrose tolerance test, consisting of administration of 2.5 gm. of dextrose per kg. of body weight. The dextrose was given in a 15 per cent solution by stomach tube, and the blood-sugar level was determined at intervals of 30 min., 1 hour, 2 hours and 3 hours. 2. The blood sugar mobilization test, consisting of a subcutaneous injection of 0.05 mg. of epinephrine per kg. of body weight, which was followed by half-hourly blood-sugar determinations over a period of 2 hours.

To check the results obtained with these two tests, a modification of the dextrose tolerance test was used in which 2.5 gm. of dextrose per kg. were given by stomach in a 5 per cent solution, and 0.5 unit of insulin per kg. of rabbit were injected subcutaneously. Epinephrine was given at the end of 3 hours, and the blood-sugar was followed for 5 hours.

The rabbits were not fasted before the tests because, in our experience (14), fasting for even 16 hours affects the carbohydrate equilibrium of these animals.

Blood-sugar determinations were made in duplicate by the method of Hagedorn-Jensen. For glycogen determinations, the rabbits were sacrificed by a blow below the occi-

put. The entire livers and the adductor longus and adductor magnus muscles were immediately removed and placed in boiling potassium hydroxide after the method of Pflüger.

## RESULTS

In the course of this work over 400 blood-sugar curves were obtained, and for brevity the following manner of presenting our data was chosen. For every curve the average blood-sugar was calculated. By subtracting the figure for the initial blood-sugar from that of the average blood-sugar, a single figure is obtained which expresses the result of the test in terms of disposal or of mobilization of sugar. For instance, the average of a blood-sugar curve obtained at 30 minute intervals after an injection of epinephrine and reading 92, 130, 138, 128 and 116 mg. per cent, is 125 mg. per cent. By subtracting the initial blood-sugar of 92 mg. from 125 mg., the result of plus 33 mg. is obtained. This figure expresses the degree of mobilization of sugar following injection of epinephrine in a given rabbit. In general, the peak of the curves paralleled this increase in the average blood-sugar, but was less reliable.

With this method of calculation, even small differences are significant because each figure represents an elevation of blood-sugar for the duration of the experiment. By averaging these figures from all rabbits for each day of the experiment, we can plot a curve that shows at a glance the effect of successive injections of a blocking substance on utilization or mobilization of sugar.

**Experiments with India ink.** 1. An initial injection of 10 c.c. of India ink was given each of 12 rabbits. This was followed by daily injections of 5 c.c. The animals were tested 16 hours after each injection. The average morning blood-sugar as seen in Chart I was lowered for a time, but eventually this effect of the injections wore off. During the dextrose tolerance test the increase in average blood-sugar at first diminished rapidly (see Chart II), but began to rise again after

Average Increase of Blood Sugar in Mg.

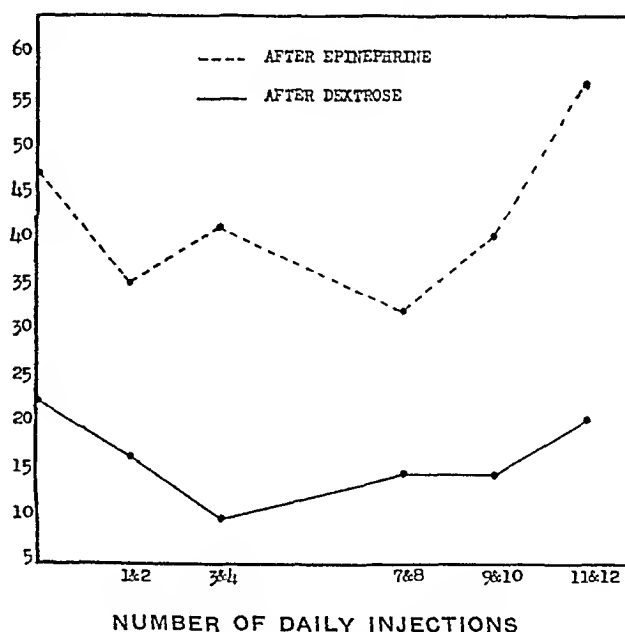


Chart II. Results of the dextrose tolerance and epinephrine tests in 12 rabbits receiving daily 5 c.c. of India ink. The tests were performed 16 hours after the injections.

## Average Increase of Blood Sugar in Mg.

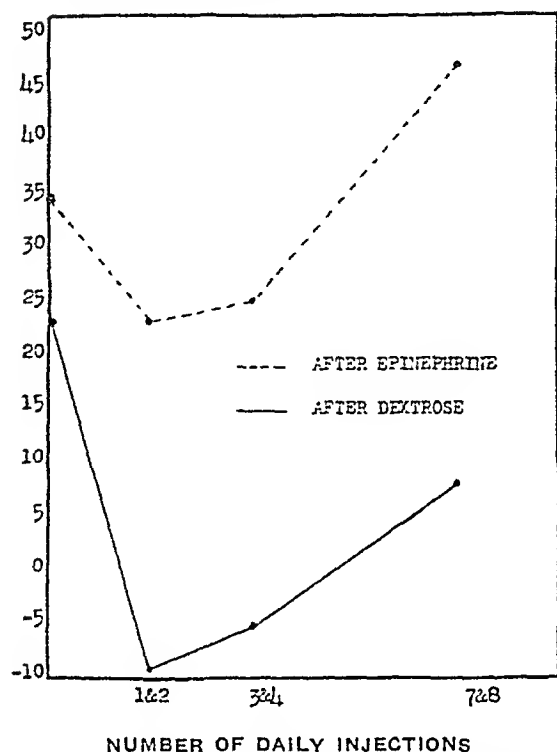


Chart III. Results of the modified dextrose tolerance test immediately followed by epinephrine in 2 rabbits receiving daily 5 c.c. of India ink. The tests were performed 16 hours after the injections.

the fourth injection and nearly reached its normal value after 12 injections. The average increment in blood-sugar was less by about 40 per cent during the first 10 injections. After that the curve became irregular, but the average was still about 13 per cent

## Average Increase of Blood Sugar in Mg.

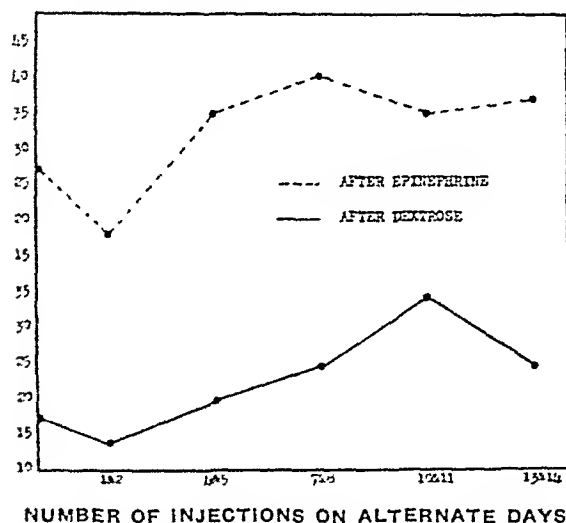


Chart IV. Results of the dextrose tolerance and epinephrine tests in 4 rabbits receiving 10 c.c. of India ink on alternate days. The tests were performed 30 minutes after injection.

lower than normal for the remainder of the experiment.

Essentially the same is true of the curve showing changes in the increment of the average blood-sugar during the epinephrine test. The maximum lowering of the blood-sugar approximately coincided with the greatest changes in dextrose utilization and blood-sugar mobilization.

Six animals in this experiment were tested at intervals after the injections of India ink were discontinued, but the curves following both tests were so irregular as to preclude interpretation. The only consistent changes were seen in the morning blood-sugars, which at first were increased above normal for several days and later fluctuated around the level observed before the experiment (Chart I).

2. Two rabbits were injected in a similar manner and subjected to the modified glucose tolerance test 16 hours after injection. Chart III shows that, under these conditions of accelerated assimilation of sugar due to insulin, the increase in dextrose tolerance was

## Average Increase of Blood Sugar in Mg.

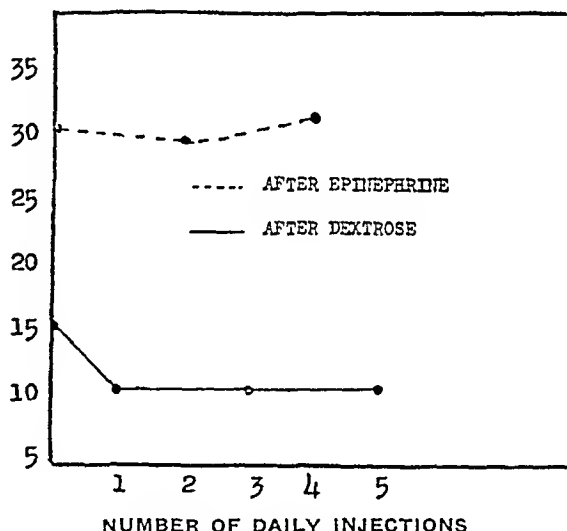


Chart V. Results of the dextrose tolerance and epinephrine tests in 4 rabbits injected daily with the carbon-free fractions from 5 c.c. of India ink. The tests were performed 16 hours after the injections.

more pronounced than in the first experiment. The decrease in mobilization of blood-sugar after injection of epinephrine was about the same. The morning blood sugar was lowered.

3. Four rabbits were injected on alternate days with 10 c.c. of India ink (twice the usual dose) for four weeks. The animals were tested 30 minutes and 24 hours after injection. At the 24 hour period the findings were similar to those obtained 16 hours after injection (see Chart II) only less marked.

At the 30 minute period, beginning with the second curve, the blood sugar tolerance curves became higher and the mobilization of blood sugar by epinephrine became greater than before the experiment (see Chart IV).

*Experiment with the carbon-free fractions of India ink.* Four rabbits were given daily injections of the combined carbon-free fractions obtainable from 5 c.c.

of India ink, and both tests were performed 16 hours after injection. During the period of injections the morning blood-sugar in this experiment was slightly higher than normal. Chart V shows only a slight change from normal in the rise of blood sugar after dextrose in these animals. Their ability to mobilize blood-sugar was unchanged.

*Experiments with graphite.* 1. Four rabbits were subjected to daily injections of 10 c.c. of a colloidal suspension of graphite for 11 days. The two tests were performed 16 hours after injection.

2. Four animals were treated in a similar way for 4 days, but only the dextrose tolerance test was done. Sixteen hours after the last injection, these rabbits were sacrificed for determination of hepatic glycogen. Four littermate control animals were kept without food in the laboratory for the same length of time as the experimental rabbits from which samples of blood were being taken. They also received the same amount of dextrose by stomach-tube as the animals undergoing the dextrose tolerance test.

Average Blood Sugar in Mg.

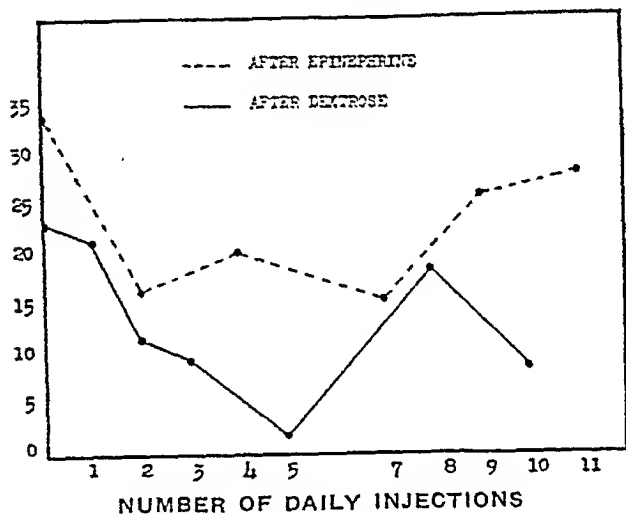


Chart VI. Results of the dextrose tolerance test in 10 rabbits and epinephrine test in 4 rabbits receiving daily 10 c.c. of colloidal graphite. The tests were performed 16 hours after the injections.

3. Four animals whose responses to the dextrose tolerance test were normal were subjected to the same regime as the rabbits in the preceding experiment. These animals, with four controls, were also sacrificed on the fourth day for determinations of the glycogen content of the liver and muscles. Tolerance to dextrose was followed in two of the injected rabbits.

The morning blood-sugar of rabbits in these experiments was lowered to the same extent as that in the first experiment with India ink. The average curves after dextrose and after epinephrine are shown in Chart VI. The changes observed following injections of India ink—namely, increased tolerance to dextrose and decreased mobilization of blood-sugar—are seen to be present to a more marked degree. For instance, increment in blood-sugar after dextrose was about 60% less than normal, as compared with the average of 40 per cent less in the experiment with India ink.

Experiments 2 and 3 (Table I, columns 1 and 2) show that hepatic glycogen was decreased in the rabbits injected with graphite. The same was true of the

glycogen content of the muscles (Table II, columns 1 and 2).

4. Four rabbits were fasted for 3 days while receiving, in the morning, graded injections of 4, 8 and 16 c.c. of colloidal graphite. Blood-sugar determinations were made in the morning and 5 hours after injection. A like number of control animals were treated

TABLE I

*The effect of reticulo-endothelial block on hepatic glycogen\**

| CONTROL RABBITS |                   | RABBITS INJECTED WITH GRAPHITE |                   |                   |                   |
|-----------------|-------------------|--------------------------------|-------------------|-------------------|-------------------|
|                 |                   | 16 hrs. previously             |                   | 5 hrs. previously |                   |
| Number          | per cent Glycogen | Number                         | Glycogen per cent | Number            | Glycogen per cent |
| 385             | 11.14             | 194                            | 8.19              | 638               | 5.85              |
| 387             | 11.02             | 386                            | 4.16              | 635               | 4.35              |
| 193             | 7.10              | 185                            | 3.61              | 639               | 3.65              |
| 390             | 5.58              | 192                            | 2.55              | 634               | 3.38              |
| 191             | 4.68              | 384                            | 1.41              | 640               | 3.28              |
| 195             | 4.48              | 190                            | 1.06              | 636               | 2.29              |
| 183             | 0.85              | 388                            | 0.99              | 637               | 1.20              |
| 389             | 0.76              | 391                            | 0.89              | 641               | 0.91              |
| Average         | 5.70              | Average                        | 2.86              | Average           | 3.10              |

\*Marked fluctuations of hepatic glycogen are usual in animals not subjected to fasting. We tried to offset this by increasing the number of animals in these experiments.

in the same way except for the injections. Chart VII shows that the blood-sugar of the blocked rabbits under fasting conditions was lower than that of the fasting controls.

5. Four rabbits were injected on consecutive days with 1 c.c. and 2 c.c. of colloidal graphite and were subjected to the dextrose tolerance test 5 hours after injection. Four more rabbits were given consecutive

TABLE II

*The effect of reticulo-endothelial block on the glycogen of muscles*

| CONTROL RABBITS |                   | RABBITS INJECTED WITH GRAPHITE |                   |                   |                   |
|-----------------|-------------------|--------------------------------|-------------------|-------------------|-------------------|
|                 |                   | 16 hrs. previously             |                   | 5 hrs. previously |                   |
| Number          | Glycogen per cent | Number                         | Glycogen per cent | Number            | Glycogen per cent |
| 193             | 0.55              | 194                            | 0.47              | 638               | 0.38              |
| 183             | 0.50              | 192                            | 0.25              | 639               | 0.34              |
| 191             | 0.40              | 185                            | 0.23              | 641               | 0.30              |
| 195             | 0.29              | 190                            | 0.18              | 640               | 0.25              |
| Average         | 0.44              | Average                        | 0.28              | Average           | 0.32              |

injections of 0.5 c.c. and 1 c.c. of this material and were subjected to the epinephrine test after the same interval. On the following morning all animals received 4 c.c. of colloidal graphite, and were sacrificed 5 hours after injection for determination of glycogen in the liver (8 rabbits) and in the muscles (4 rabbits).

Chart VIII shows that the effects of a small dose of our blocking substance on dextrose tolerance and on blood-sugar mobilization were opposite to those of larger doses. The blood-sugar was raised in most instances. Tables I and II (columns 3) show that the glycogen content of the liver and muscles was reduced.

In none of the experiments with India ink or with graphite were toxic symptoms observed. Except in the experiment in which the rabbits were fasted, they

maintained their weight or continued to grow during the period of injections.

### COMMENT

Partial block of intravascular reticulo-endothelial cells, as shown by our data, produces five phenomena in the realm of carbohydrate metabolism: 1. Depression of the blood-sugar under conditions of normal food intake (Chart I) and during fasting (Chart VII). 2. Lowering of the blood sugar curve following ingestion of dextrose (Charts II and VI), which was accentuated by administration of insulin (Chart III). 3. Decreased mobilization of blood-sugar by epinephrine (Charts II and VI).<sup>\*</sup> 4. Reduction in hepatic glycogen (Table I). 5. Diminution in the glycogen of the muscles (Table II).

We believe that these changes are due to physical block and not to a toxic effect of India ink, because colloidal graphite gave results similar to those obtained with India ink (Charts II and VI). On the contrary, the combined carbon-free fractions of India ink failed to produce such changes (Chart V). We ascribe the observed metabolic deviations to impairment in function of the reticulo-endothelial system because a small dose of graphite which, according to the accepted view, should have caused irritative hyperfunction of the reticulo-endothelial cells raised the blood-sugar and produced higher blood-sugar tolerance curves and increased mobilization of blood-sugar (Chart VIII). These effects are the reverse of those observed after larger doses of our blocking substances. An independent study by one of us (B.E.B.) on immunity reactions in experimental Brucella infection following similar doses of India ink resulted in the death of half

Blood Sugar in Mg.

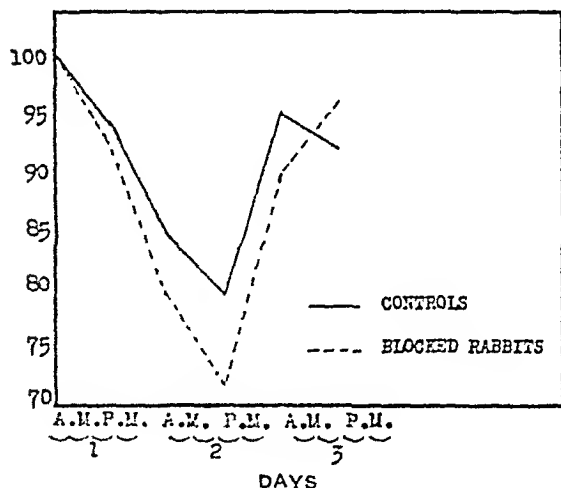


Chart VII. Blood sugar of 4 fasting rabbits injected on successive days with 4, 8 and 16 c.c. of colloidal graphite and of their fasting controls (4). Specimens were obtained before and 5 hours after each injection.

of the rabbits. The surviving animals showed more pronounced toxic symptoms than the infected controls among which there were no deaths (15). This indi-

<sup>\*</sup>We assume that the lower curves after injection of epinephrine are not in the main due to increased tolerance of mobilized sugar, because in individual animals they did not necessarily correspond in time or degree to changes in the dextrose tolerance test.

cated that at least one other function of the reticulo-endothelial cells was depressed under the conditions of our experiment.

Our data on the effect of reticulo-endothelial block on carbohydrate metabolism were, we believe, obtained

Average Increase of Blood Sugar in Mg.

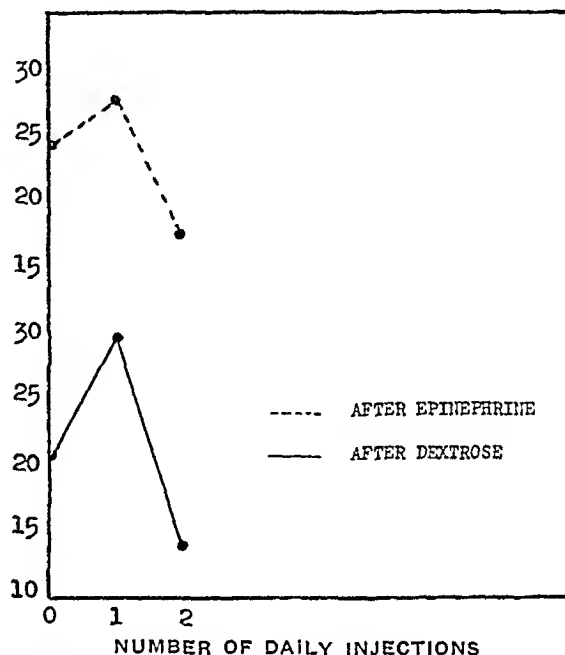


Chart VIII. The effects of small doses of colloidal graphite on the dextrose tolerance (4 rabbits injected on successive days with 1 c.c. and 2 c.c.) and on the epinephrine test (4 rabbits given similarly 0.5 c.c. and 1 c.c.) 5 hours after injection.

from a large enough number of rabbits studied over a sufficient length of time to minimize the significance of individual variations. Our interpretation of these findings rests in part on conjecture, and therefore is subject to revision.

The phenomena enumerated may be caused directly by interference of accumulated carbon particles with the function of the affected reticulo-endothelial cells, if we assume with other writers that these cells in the aggregate act as a distinct metabolic organ producing intracellular chemical changes in fats, proteins and carbohydrates. On the other hand, it is possible that block of reticulo-endothelial cells may produce these changes indirectly by influencing other organs of metabolism with which these cells are in close anatomical relationship.

In considering the second possibility, we know from the literature (9, 11, 16) and from our own histological observations, that deposition of particles after injection of India ink or of colloidal graphite takes place chiefly in the reticulo-endothelial cells of the liver, and to a lesser degree in those of the spleen and bone-marrow. Since the spleen and bone-marrow have no established function in the metabolism of carbohydrates, we have confined our attention to the liver.

The deviations observed in carbohydrate metabolism cannot be explained by irritation of the hepatic parenchyma with resulting hyperactivity of the liver, be-



cause previous experience (17) has taught us that hepatic hyperfunction is manifested by *increased* tolerance to dextrose and by *increased* mobilization of blood-sugar after injection of epinephrine. Nor can the characteristic changes following block be accounted for by hepatic insufficiency which would result in *decreased* tolerance to dextrose and in *decreased* mobilization of blood-sugar by epinephrine (5, 6).

The combination of *increased* tolerance to dextrose and of *decreased* mobilization of blood-sugar following epinephrine could be due to an insufficient production of sugar in the liver. This organ normally converts sufficient amounts of non-carbohydrate substances into glycogen to fill the gap between the intake of carbohydrates and the energy requirements of the body. In the case of man the liver thus supplies from its own resources about half of the daily internal need for sugar (18). Interference with this function of the liver would lead to an internal deficiency of sugar, thus accounting for lowering of the blood-sugar in blocked fed rabbits and for greater lowering of the blood-sugar in blocked fasting animals than in fasting controls. On the same basis, increased sugar tolerance would be explained partly by an increased sugar vacuity in the tissues and partly by greater inhibition of hepatic gluconeogenesis after administration of dextrose. The latter explanation rests on a demonstration by Soskin (19) that administration of dextrose inhibits gluconeogenesis in the liver and that the degree of inhibition is inversely proportional to the extent of gluconeogenesis. Diminution in the glycogenolytic response to epinephrine is explained by decreased gluconeogenesis and consequent lowering of the glycogen content of the liver. Reduction in the glycogen content of muscles logically follows diminished production of sugar by the liver, with consequent depletion of carbohydrates in the body.

The mechanism of reduced production of sugar on the part of the liver is explicable if it can be shown that the Kupffer cells, which together with ordinary endothelial cells line the hepatic sinusoids, act as a transmitting agent of molecular substances from the blood to the liver. In such a case, block of these cells would curtail the supply of materials from which the liver makes sugar. Evidence that the Kupffer cells have the function of transmitting certain substances to the liver, is furnished by the work of Grossmann (20) and of Radt (21) who showed that previously injected India ink decreases the toxic action of chloroform on the hepatic parenchyma. Jungeblut and McGinn (22) demonstrated that reticulo-endothelial block retards the absorption of arsphenamine from the blood and at the same time reduces the arsenic content of the liver. Higgins and Murphy (11) state that in hemosiderosis iron is transferred directly from the Kupffer cells to the liver.

The Kupffer cells take a similar part in at least some phases of carbohydrate metabolism. Koster, Goldzieher and Collens (23) described changes indicative of enhanced functional activity in the Kupffer cells following administration of dextrose. Gaessler (24) showed that reticulo-endothelial block retards the utilization of injected lactic acid which normally is promptly taken up by the liver and transformed into sugar. *This is a specific instance of failure on the part of a precursor of glycogen to reach the liver in blocked animals.* Finally, Freund (25) found that preliminary fasting leads to increased deposition of in-

jected colloidal particles in the Kupffer cells, while an abundance of glycogen in the liver leads to lessened deposition of such particles in these cells. The last work is of great significance to us because it indicates that *the glycogen content of the liver is a determining factor in the absorptive activity of the Kupffer cells*, which according to our hypothesis furnish the liver with precursors of glycogen from the blood.

Starvation and reticulo-endothelial block have in common lowering of the blood-sugar, reduction in hepatic and muscle glycogen, diminished mobilization of blood-sugar following injections of epinephrine, and decreased threshold for the appearance of acetone bodies in the blood (26). Depletion of carbohydrates, common to both conditions, determines these similarities.

Starvation differs from block in causing decreased instead of increased tolerance to dextrose. This difference is explained by the fact that in starvation the organism is cut off from exogenous carbohydrates\*, but the liver has free access to the fat and protein stores of the body, with a resulting increase in gluconeogenesis which according to Soskin it is difficult to inhibit by administration of dextrose. In block, a normal food supply reaches the blood from the alimentary tract, but there is a partial barrier separating the liver from substances with which to manufacture sugar. Decreased gluconeogenesis which is readily inhibited by giving of dextrose is the result. This explanation is supported by our observation that block brings about an additional lowering of the blood-sugar in fasting rabbits (Chart VII). The additional lowering of the blood-sugar would probably be more marked in a species which, unlike the rabbit, does not have in its alimentary canal considerable amounts of food residues to draw upon even after remaining without food for three days. Our theory on the action of reticulo-endothelial block falls in with the experiments in the preceding papers of this series, showing the influence of hepatic changes on dextrose tolerance; and with those of Soskin, Allweiss and Cohn (27) which prove that the liver and not, as previously thought, the pancreas is essential to the metabolic reactions which determine the normal dextrose tolerance curve.

Can the conception of the Kupffer cells as a transmitting agent be applied to the metabolism of fats and proteins? A complete review of this subject is beyond the scope of the present paper. Moreover the all too frequent use of insufficient amounts of blocking substance, of toxic substances, and of insufficient numbers of animals precludes the possibility of ever fitting the mass of contradictory findings into one conception. However, our hypothesis is consistent with several recent investigations. Outstanding among these is the work of Leites showing that neutral fats and fatty acid are changed to cholesterol in the liver (28), and that reticulo-endothelial block decreases the amount of cholesterol in the blood which leaves the liver through the hepatic veins (29). Hypocholesterinemia in the systemic circulation after block was observed by Leites (30), by Klein and Levinson (2), and by Goebel and Gnoinski (31). Jaffé (11) demonstrated that the Kupffer cells may engulf large quantities of lipid from the blood-stream, and subsequently transfer it to the adjacent hepatic cells.

\*Decreased tolerance to dextrose does not depend on lack of nutrition *per se* because it also follows exclusive fat or protein diets.

In the realm of protein metabolism, Chrometzka (32) found that injections of India ink markedly interfere with the hepatic function of converting uric acid into allantoin in dogs. As would be expected, with depression of several functions of the liver due to shortage of materials for its "metabolic mill," the respiration of hepatic cells was found by Jungeblut and Berlot (33) to be markedly impaired after block.

Against the concept of reticulo-endothelium playing a distinct metabolic role, we wish to offer its histological appearance. The cells of this system possess so little cytoplasm that it is difficult to visualize them performing intracellular chemical transformations in the metabolism of carbohydrates, fats and proteins in addition to their functions of phagocytosis and formation of immune bodies.

There is little additional comment required by our experimental data. Since the effect of multiple injections

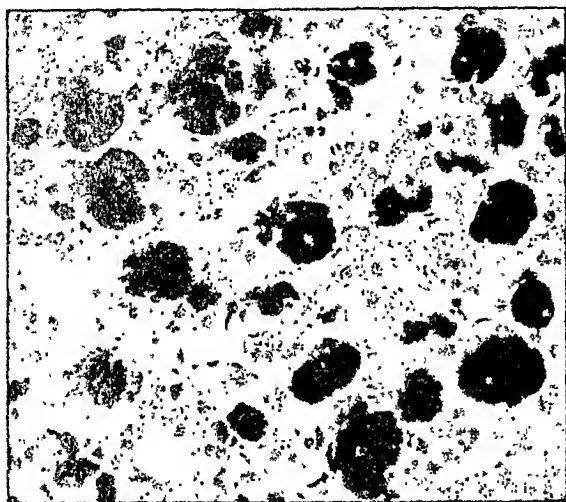


Fig. 1. Liver of a rabbit subjected to daily injections of 5 c.c. of India ink for 3 weeks. The section shows a great increase in the number and size of Kupfer cells. By focusing the microscope at different levels the black masses in the dilated sinusoids are seen to consist of up to 20 mononuclear cells. The cytoplasm of these cells is filled with carbon particles while the nucleus is usually pushed to the periphery. A number of multinucleated forms are observed. X 250.

tions of a blocking substance is in dispute, it is interesting to note that the curves representing utilization of dextrose and mobilization of blood-sugar after block (Charts II and V) indicate that the first few injections had a cumulative effect. Subsequent injections caused progressively diminishing changes. The explanation of this lies in increased proliferation of the reticulo-endothelial cells after block, described by Aschoff and others (34-37). Under such conditions, Derman (38) observed particularly active multiplication in the Kupfer cells of the liver, which we were able to confirm from our microscopic studies (see Figure 1).

The irregular response of rabbits to the dextrose and epinephrine tests after injections of India ink were discontinued has its parallel in a similar irregularity during recovery from experimental chloroform poisoning observed by one of us (T.L.A.) (6). The recovery from block is expressed by consistent changes in the morning blood-sugar which, at first, indicate increased hepatic activity and later a return to the level

maintained before the beginning of injections (Chart I). Temporary hyperfunction of organs recovering from injury or following a period of unusual activity associated with hypertrophy, is a well-known phenomenon.

The reduced tolerance to dextrose and increased mobilization of blood sugar after epinephrine in rabbits injected with India ink 30 minutes previously (see Chart IV) is another example of this. The higher than normal blood sugar curves in these animals are due to lessened inhibition of gluconeogenesis by dextrose because gluconeogenesis was more active 48 hours after the preceding injection due to hyperactivity of the regenerated Kupfer cells in supplying precursors of glycogen to the liver. This explanation is supported by the fact that the first 30 minute curves were not higher but lower than normal, because there was no preceding 48 hour injection.

### SUMMARY

Partial block of intravascular reticulo-endothelial cells causes lowering of the blood-sugar, increased tolerance to dextrose, decreased mobilization of blood-sugar by epinephrine and reduction in the glycogen content of the liver and muscles.

These findings are interpreted as indicating that one of the functions of the Kupfer cells is the transmission of precursors of glycogen from the blood stream to the liver. Block of these cells interferes with such a transfer and results in decreased gluconeogenesis and consequent internal deficiency of carbohydrates, which explains the observed abnormalities.

A review of available experimental data on the effects of reticulo-endothelial block in the metabolism of fats and proteins also suggests that this system acts as a transmitting agent of intermediary metabolites from the blood to the liver and perhaps to other organs rather than as a separate metabolic organ.

### REFERENCES

1. Sterkin, E. J., and Kerner-Posehenjan, E. L.: Zur Frage des Einflusses einer Blockade des Retikuloendothelialsystems auf den Blutzuckerspiegel. *Ztschr. f. d. ges. exper. Med.*, 64:311, 1929.
2. Klein, R. I., and Levinson, S. A.: Effect of Reticulo-Endothelial Blockade on Blood Chemistry. *Proc. Soc. Exp. Biol. and Med.*, 31:353, 1933.
3. Nakaya, K.: On the Biological Significance of the Reticulo-Endothelial System in the Formation of Glycogen. *Nika Z.*, p. 195, 1927.
4. Messina, R.: Ipoglicemia e reticulo-endotelio. *Archivio di farmacologia sperimentale*, 52:197, 1931.
5. Althausen, T. L., and Thoenes, E.: Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes. II. Phosphorus Poisoning. *Arch. Int. Med.*, 50:58, 1932.
6. Althausen, T. L., and Thoenes, E.: Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes. III. Chloroform Poisoning. *Ibid.*, 50:257, 1932.
7. Jaffe, R. H.: Reticulo-Endothelial System in Immunity. *Physiological Reviews*, 11:277, 1931.
8. Cannon, P. R.; Macer, R. H.; Sullivan, F. L., and Webster, J. R.: The Influence of Blockade of the Reticulo-Endothelial System on the Formation of Antibodies. *Trans. Chicago Pathol. Soc.*, 13: 215, 1930.
9. Pratt, D. W.: Experimentelle Untersuchungen über die Kardiokarwinde der Leber die die Produktion der Retikuloendothelialen zu ihnen, nebst Beobachtungen über die Wirkung der Kupferzellen in der Leber. *Arch. f. exp. Med.*, 1927.
10. Victor, J., Van Buren, J. R., and Smith, H. P.: Studies on Vital Staining. IV. India Ink and Brilliant Vital Red. Importance of Considering Liver Excretion in the Study of "Blockade of the Reticulo-Endothelial System." *J. Exper. Med.*, 51:531, 1930.
11. Higgins, G. M., and Murphy, G. T.: The Phagocytic Cells (v. Kupfer) in the Liver of Common Laboratory Animals. *Anat. Record*, 40:15, 1928.
12. Leites, S., and Rabinow, A.: Zur Frage der Blockade des reticuloendothelialen Systems und dessen funktioneller Prüfung. *Ztschr. f. d. ges. exp. Med.*, 54:314, 1927.
13. Danner, L.; Ostertag, B., and Lücke, H.: Insulinkrämpfe und reticuloendotheliales System. *Kl. W.*, 13:101, 1934.
14. Althausen, T. L., and Thoenes, E.: Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes. I. Fasting and Administration of Thyroxine. *Arch. Int. Med.*, 50:46, 1932.

15. Blomquist, B. E.: Studies on the Histogenic Immunity Reaction in Experimental Brucella Infections. Master of Arts Thesis in Bacteriology. University of California, September, 1933.
16. Nagao, K.: Fate of India Ink Injected into the Blood. *J. Inf. Dis.*, 27:527, 1920.
17. Althausen, T. L.; Lucia, S. P., and Rinehart, J. F.: Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes. V. Cirrhosis of the Liver. In preparation.
18. Althausen, T. L.: Dextrose Therapy in Diseases of the Liver. *J. A. M. A.*, 100:1163, 1933.
19. Soskin, S.: Personal communication.
20. Grossmann, F.: Über das Verhalten der Leberzellen bei vitaler Speicherung. *Frankf. Z. Path.*, 36:635, 1928.
21. Rndt, P.: Über die körnige Ablagerung kolloider Farbstoffe in den Leberparenchymzellen von Kaninchen nach intravitraler Injektion (nach Versuchen mit Tusche und Eisen). *Ztschr. f. d. ges. exp. Med.*, 69:721, 1930.
22. Jungeblut, C. W., and McGinn, B. R.: The Role of the Reticulo-Endothelial System in Immunity. VI. The Effect of Endothelial Blockade on the Storage and Distribution of Neocarphenamine. *J. Exp. Med.*, 51:5, 1930.
23. Koster, H.; Goldzieher, M. A., and Collens, W. S.: The Effect of Intravenous Injection of Dextrose on the Kupfer Cells of the Liver. *Arch. Path.*, 9:197, 1930.
24. Gaessler, E. O.: Zur Frage der Beteiligung des Reticuloendothels der Leber an der Resynthese der Milchsäure. *Ztschr. d. ges. exp. Med.*, 69:105, 1930.
25. Freund, R.: Das Problem des reticulo-endothelialen Systems. *Virchow's Arch. f. path. Anat.*, 256:326, 1932.
26. Leites, S., and Wodinsky, M. A.: Alimentäre Stoffwechselreaktionen: VI. Stoffwechselreaktionen auf Peptonzufuhr bei "Blockade" des Reticulo-Endothelialsystems. *Ztschr. f. d. ges. exp. Med.*, 80:726, 1932.
27. Soskin, S.; Allweiss, M. D., and Cohn, D. J.: Influence of the Pancreas and the Liver upon the Dextrose Tolerance Curve. *Am. J. Physiol.*, 103:153, 1934.
28. Leites, S.: Studien über Fett- und Lipidstoffwechsel. I. Mitteilung: Über alimentäre Lipämie. Die Beziehungen zwischen Neutralfett und Lipoiden in der Norm und bei Belastung mit Neutralfett bzw. Oleinsäure. *Biochem. Ztschr.*, 184:273, 1927.
29. Leites, S.: Studien über Fett- und Lipidstoffwechsel. V. Mitteilung: Über die Rolle der Milz im Fett- und Lipidstoffwechsel. *Biochem. Ztschr.*, 186:336, 1927.
30. Leites, S.: Studien über Fett- und Lipidstoffwechsel. IV. Mitteilung: Über die Rolle des reticulo-endothelialen Systems im Fett- und Lipidstoffwechsel. *Biochem. Ztschr.*, 186:331, 1927.
31. Goebel, F., and Gneinski, H.: Le métabolisme de la cholestérine et le système réticulo-endothélial. *Comp. Rend. Soc. de Biol.*, 96:1453, 1927.
32. Chrometzka, F.: Beeinflussung des Purinstoffwechsel des Hundes durch Blockade des reticulo-endothelialen Systems mit Tusche. *NL Wochschr.*, 12:1968, 1933.
33. Jungeblut, C. W., and Berlot, J. A.: The Role of the Reticulo-Endothelial System in Immunity. II. The complement Titer after Blockade and the Physiological Regeneration of the Reticulo-Endothelial System as Measured by Reduction Tests. *J. Exper. Med.*, 43:797, 1926.
34. Aschoff, L.: Das reticulo-endotheliale System. *Erg. d. inn. Med. u. Kinderh.*, 26:1, 1924.
35. Davies, F. B.; Wadsworth, R. C., and Smith, H. P.: Studies on Vital Staining: V. Double Staining with Brilliant Vital Red and Nigra Sky Blue. Correlation of Histological and Physiological Data. *J. Exp. Med.*, 51:549, 1930.
36. Wein, S., and Sümei, S.: Untersuchungen über die Funktion des mit Eisen blockierten reticulo-endothelialen Apparates. *Wien. Arch. f. inn. Med.*, 10:457, 1925.
37. Lemmel, A., and Löwenstätt, H.: Das Verhalten blockierter Zellen in Mixeplantaten nach vitaler Tuschespeicherung. *Arch. f. exper. Zellforsch.*, 3:10, 1926-27.
38. Derman, G. L.: Experimentell-morphologische Beiträge über die sog. "Blockade" des reticuloendothelialen Systems. *Virchow's Arch. f. path. Anat. u. Physiol.*, 267:73, 1928.

## DISCUSSION:

DR. LAY MARTIN (Baltimore, Md.): This paper, as you are well aware, is an extremely interesting one, especially, since the reticulo-endothelial system does not readily lend itself to investigation.

It is generally conceded that the reticulo-endothelial cells are strongly phagocytic and have much to do with the breakdown of hemoglobin into bilirubin, beyond this, there is little, if any, knowledge of their function. Dr. Althausen has well described the complex and uncertain state of conjecture that surrounds their other metabolic activities and I congratulate him, not only for his temerity in treading on this unpromising field, but also for his open minded attitude.

The Kupfer cells of the liver are bathed by serum in the hepatic sinusoids and it is difficult to see how there can be any direct passage from them to liver cells. Any product from them would be as apt to be swept into the general

circulation as into the hepatic cells. The question of direct transfer from these cells into hepatic cells is quite unproven physiologically and difficult to understand from their anatomical arrangement.

From the data presented, Dr. Althausen has drawn certain conclusions as to the rôle of the reticulo-endothelial system in carbohydrate metabolism. The data are collected from the results of sugar tolerance tests and epinephrine produced blood sugar responses in rabbits which had previously received repeated intravenous injections of India ink and graphite. The injections were made with the idea that the reticuloendothelial cells, once filled with the material, would be, in part or wholly, removed from normal functional activity.

My first criticism of the paper is in reference to control determinations. Little mention is made of them in the article and, judging from the figure, I take it that only one estimation of sugar tolerance and of epinephrine response was made on each animal. I feel it most important that as many tests be made before the intravenous injection of the blocking material as after. It seems likely to me that in this case, the controls might show the same variations as the test animals.

My second criticism centers on the question of the interpretation of the increased sugar tolerance and the decreased epinephrine response which are described.

When sugar is absorbed by the body, it may be disposed of in several ways.

- I. changed into glycogen in the liver or muscles;
- II. stored in the tissue fluids;
- III. oxidized;
- IV. excreted in the urine.

If there is any lowering of the ability of the body to handle sugar, it will at first accumulate in the blood. Dr. Althausen has presented no evidence that there is any increased storage of sugar in the tissue, nor that the oxidative processes are heightened nor that there is glucosuria. If the liver cannot change glucose to glycogen, it should pile up in the blood. If the reticulo-endothelial system is blocked and it is responsible for the transfer of glucose to the liver again, blood glucose should increase. However, according to Dr. Althausen's figures, it decreases. I do not see that Soskin's experiments to which Dr. Althausen refers, are german to the points under discussion.

The figures show a decrease in epinephrine response which the investigator believes to be due to decreased liver and muscle glycogen; this decrease being secondary to lowered carbohydrate metabolism following the block of the reticulo-endothelial cells. As epinephrine causes a breakdown of muscle glycogen into lactic acid, there should be an increased amount of blood lactic acid. Furthermore, if Gaessler's interpretation of his own experiments are correct and the reticulo-endothelial cells also control the transfer of lactic acid to the hepatic cells, there should be an even greater increase of blood lactic acid. The present investigations do not attempt to go into this point but it seems to me worthy of study.

The authors figures on the determination of liver and muscle glycogen are worthy of consideration. You will note that in each instance there is a tremendous variation in the liver and muscle glycogen storage in both the control and test determinations.

As Dr. Althausen has mentioned, the work is still in its early stages and much remains to be determined in this very interesting field.

DR. RALPH C. BROWN (Chicago, Ill.): It seems to me that Dr. Althausen and his associates have presented some very interesting data in this paper. They have apparently shown that there is an increased sugar tolerance with a decreased response to epinephrine after the blocking of the reticulo-endothelial system with carbon pigment. As they and many other workers have pointed out, the individual variations in the response of the experimental animals and the opposite effects produced by small and large doses of blocking substances make interpretation of results difficult. Dr. Althausen has shown in some of his curves that, despite continued administration of the blocking substance, a return toward normal occurs, suggesting, perhaps, a proliferation of the reticulo-endothelial system more rapid than the block. It would have been interesting to have followed and correlated the histologic hyperplasia with the return of normal metabolic function. The very great proliferative capacity of the cells of the reticulo-endothelial system has been shown by Weiss and Sümegi of Buda Peste in their extensive series of experiments designed to demonstrate the rôle of the reticulo-endothelial system in the production of bilirubin.

This work adds further evidence to the steadily gaining conception of the importance of the rôle of the liver in carbohydrate metabolism. The work of Soskin and his associates with normal, depancreatized, and hepatectomized dogs has suggested that the form of the dextrose tolerance curve is in the main dependent upon the liver. They stress the importance of the regulatory mechanism whereby a certain level of hyperglycemia causes the liver to cease gluconeogenesis. It seems probable to these workers that a condition of high metabolic activity in the liver results in a less sensitive response, a failure on the part of the liver to cease gluconeogenesis, and a consequent high sugar tolerance curve. On the contrary, in a liver wherein the metabolic activity is proceeding slowly, the regulatory mechanism is sensitive, gluconeogenesis ceases promptly with even mild hyperglycemia, and a lowered sugar tolerance curve is obtained.

The correlation of this work with the present experiments is possible. An explanation in this light would imply the following possible train of events. As a result of the block of the reticulo-endothelial system, fewer precursors of glucose are available to the liver. The liver operates at a lower metabolic level than normal. As a consequence there is a low sugar tolerance curve. The authors have suggested that there is a glycogen debt in the tissues which is responsible for the low tolerance. They have shown this by glycogen determinations upon the muscles. It is possible, however, that this may not be the operating factor in depressing the tolerance curve since in those conditions where there is a marked depletion of muscle glycogen, such as the state following violent exercise, the tolerance curve is distinctly high.

The failure to respond fully to epinephrine following block, coupled with the low glycogen content of the liver make Dr. Althausen's suggestion that gluconeogenesis fails because of an insufficient supply of the precursors of glycogen very plausible. This blockade not only affects the precursors of glucose but, as the authors have stated, other substances such as chloroform, arsphenamine, and injected

lactic acid. Necessarily the suggestion that the Kupffer cells act as transfer agents in the liver can remain only a suggestion. It seems, however, that it is a very possible explanation of the phenomena which are observed.

The method of computing mean changes in the level of blood sugar will necessarily give rather crude approximations. With the many other variables which are almost impossible of control, however, it seems certain that the results are significant. The same criticism could be made of the methods of glycogen determination. In any experiment of this type the use of more control animals is highly desirable.

This work has further established the importance of the liver in the metabolism of the carbohydrates and in particular the importance of the reticulo-endothelial system in hepatic carbohydrate metabolism.

DR. T. L. ALTHAUSEN (San Francisco, Calif., in closing): I am afraid that Dr. Martin and I cannot at present compose our differences of opinion. Dr. Martin thinks that the Kupffer cells lie within closed capillaries of the liver. I believe with the German School that the Kupffer cells form a part of the endothelial wall of the sinusoids and, therefore, are in direct contact with the hepatic parenchyma. The Germans are so much impressed by the intimate relationship of the Kupffer cells with the hepatic cells proper that some of them speak of these two types of cells as forming a functional unit, the "hepaton." I don't want to go that far, but I do think that there is a close relationship between these structures, and I fail to see any difficulty in the transfer of substances from the Kupffer cells to the liver. Moreover, such a transfer as mentioned in our paper has been demonstrated by other workers to take place in regard to chloroform, arsphenamine, iron, and lactic acid.

The second question on which we seem to differ is the conditions governing gluconeogenesis. I am glad that Dr. Brown brought Soskin's work into this discussion, because on my way to this meeting I had a talk with Dr. Soskin, which brought us to the conclusion that his latest work in this field and the here reported experiments fit like pieces of a jig saw puzzle. According to Soskin's theory, gluconeogenesis from non-carbohydrate substances normally occurs in the liver. Administration of sugar tends to inhibit this gluconeogenesis. When this process is active, it is difficult to inhibit. When gluconeogenesis is proceeding at a slow rate, it is easily inhibited.

Our finding of low blood sugar curves after the dextrose tolerance test in blocked animals we at first explained, solely by an increased sugar vacuum in the tissues, due to a deficiency of carbohydrate in the body. After learning of the latest work of Dr. Soskin, we agree with him that the low blood sugar curves are at least in part due to the fact that fewer precursors of glycogen reach the liver and that gluconeogenesis, therefore, is proceeding at a slow rate and is easily inhibited by administration of sugar.\*

As for controlling our experiments: The large number of curves obtained and our method of computing results by spreading the peak of the curve over the two or three hours of the experiment, eliminate to a large extent chance variations. The experiment with the carbo-free fractions of India ink also serves as a control.

\*After the meeting, Dr. A. C. Ivy informed Dr. Day that workers in his laboratory obtained low sugar tolerance curves in dogs with an Eck fistula. This is another case where fewer precursors of glycogen reach the liver due to diversion of the portal blood from the liver.

# Studies on Crystalline Vitamin B<sub>1</sub>: Observations in Diabetes\*

By

MARTIN G. VORHAUS, M.D.

ROBERT R. WILLIAMS, M.S.

and

ROBERT E. WATERMAN, B.S.

NEW YORK CITY, NEW YORK

## INTRODUCTION

FOR some time, there has been considerable speculation upon a possible relationship between the carbohydrate metabolism and a deficiency of vitamin B<sub>1</sub>. It has been observed that when a deficiency of any vitamin is induced experimentally in animals, there may be a concomitant disturbance in the utilization of carbohydrates. Some commentators hold that this is a non-specific effect; but the bulk of accumulating evidence (1, 2, 3, 4) indicates that the carbohydrate metabolism invariably is deranged to a marked extent in B<sub>1</sub> avitaminosis.

## PREVIOUS EXPERIMENTS IN ANIMALS

Abderhalden and his workers (5, 6) demonstrated a rise in the blood sugar and glycogen content of the liver and tissues in animals which had been deprived of vitamin B<sub>1</sub>. These aberrations of the carbohydrate metabolism were most marked at the beginning of the convulsive stage of the deficiency and could be intensified by a diet rich in carbohydrates. To prevent them, not only carbohydrates but protein and glycerin had to be eliminated from the diet. It was frequently possible to abolish convulsions in animals on the usual diet by the administration of small amounts of B<sub>1</sub>, such as 0.2 grams of dried yeast daily. When the diet was rich in carbohydrates, however, the addition of this amount of B<sub>1</sub> was not sufficient to prevent the appearance of convulsions. In general, adequate quantities of B<sub>1</sub>, in the form of dried yeast, resulted not only in the disappearance of symptoms but in the return of the blood sugar and glycogen levels to normal.

The influence of insulin in vitamin B<sub>1</sub> deficiency (7) has been remarked. Although Kauffmann-Cosla and his collaborators (8) at first believed that the action of insulin reproduced the effects of the vitamin in this condition, subsequently they found (9) that its only results were to modify the blood sugar and blood carbon dioxide levels. In spite of the administration of insulin, the typical manifestations of experimental beriberi continued to develop and their animals died; but they did not, at death, show the high blood sugar values usually found.

Working along somewhat different lines, Braier (10) demonstrated that dogs which had undergone hypophysectomy previously did not present the usual increase in blood sugar when brought to a state of vitamin B<sub>1</sub> deficiency. In this respect, these dogs showed a similarity to the insulin-treated animals.

Development of the B<sub>1</sub> deficiency state in animals is accompanied by a progressive and proportionate diminution in the carbohydrate tolerance (8). Large amounts of glucose in the diet modify the course of the deficiency state to the point where their intake is followed by severe toxic manifestations, convulsions and death (11).

## CHEMICAL OBSERVATIONS

In addition to experimental studies in animals which indicate a relationship between vitamin B<sub>1</sub> and the carbohydrate metabolism, some highly significant chemical observations have been reported. Peters and his collaborators noted certain striking dissimilarities between the tissues of normal pigeons and those deprived of vitamin B<sub>1</sub> (12). According to their experiments, minced brain tissue of the avitaminous animal *in vitro* has not so great a capacity to utilize oxygen as that of the normal: the oxygen take-up is less. Upon the addition of crystalline vitamin B<sub>1</sub> to the test tube, however, there was a significant increase in the oxygen take-up of the avitaminous tissue as compared with the normal. The addition of lactates known to be formed from glucose enhanced this effect, which reached its maximum at a pH of 7.3. Pyrophosphate and α-glycerophosphate produced a further increase; while cyanide and fluoride, on the other hand, abolished the augmented take-up of oxygen resulting from the vitamin B<sub>1</sub> crystals.

Further studies (13) indicated that this effect was independent of malnutrition since the capacity of minced brain from a normal pigeon to take up oxygen was not modified by the addition of crystalline vitamin B<sub>1</sub>. Experiments with the skeletal muscle, heart muscle and liver of the avitaminous pigeons failed to produce the effect *in vitro* noted in the minced brain (14); but the minced kidney tissue from the same animals, under the same conditions, did show a statistically significant increase in the oxygen take-up. No studies have been reported as yet of the effect of vitamin B<sub>1</sub> upon minced pancreatic tissue.

Careful chemical analysis (15) of the minced brain of the avitaminous pigeon demonstrated the presence of pyruvic acid, absent in the normal minced brain. This disappeared, concomitantly with the increased oxygen take-up, upon the addition of crystalline vitamin B<sub>1</sub>.

These workers conclude (16) that the state of vitamin B<sub>1</sub> deficiency is accompanied by derangement of the lactate system of cellular metabolism, at least in the brain and kidney cells, and that the addition of

\*Presented at the 38th Annual Session of the American Gastro-Enterological Association, Atlantic City, N. J., June 10-11, 1935.  
Approved by the Publications' Committee of the Association.



| DATE  | WEIGHT | CALORIES | PROTEIN   | FAT | CARBOHYDRATE | AVAILABLE GLUCOSE | INSULIN | VITAMIN | BLOOD SUGAR | GMS. URINE SUGAR<br>PER 21 HOURS | CASE NO. 1—L. D.<br>Hospital No. 48362 | REMARKS                                            |
|-------|--------|----------|-----------|-----|--------------|-------------------|---------|---------|-------------|----------------------------------|----------------------------------------|----------------------------------------------------|
| 1934  |        |          |           |     |              |                   |         |         |             |                                  |                                        |                                                    |
| 6/7   |        | 1050     | 50        | 50  | 100          | 130               |         |         | 216         | +                                |                                        |                                                    |
| 8     |        | "        | "         | "   | "            | "                 |         |         |             |                                  |                                        |                                                    |
| 9     |        | "        | "         | "   | "            | "                 |         |         |             |                                  |                                        |                                                    |
| 10    |        | "        | "         | "   | "            | "                 |         |         | 214         | +                                |                                        |                                                    |
| 11    | 155    | "        | "         | "   | "            | "                 |         |         |             |                                  |                                        |                                                    |
| 12    |        | "        | "         | "   | "            | "                 |         |         |             |                                  |                                        |                                                    |
| 13    |        | "        | "         | "   | "            | "                 |         |         |             |                                  |                                        |                                                    |
| 14    |        | "        | "         | "   | "            | "                 |         |         |             |                                  |                                        |                                                    |
| 15    | 155    | "        | "         | "   | "            | "                 |         |         |             |                                  |                                        |                                                    |
| 16    |        | "        | "         | "   | "            | "                 |         |         |             |                                  |                                        |                                                    |
| 17    |        | "        | "         | "   | "            | "                 |         |         |             |                                  |                                        |                                                    |
| 18    | 153    | "        | "         | "   | "            | "                 |         |         | 236         |                                  |                                        |                                                    |
| 19    |        | "        | "         | "   | "            | "                 |         |         |             |                                  |                                        |                                                    |
| 20    |        | "        | "         | "   | "            | "                 |         |         |             |                                  |                                        |                                                    |
| 21    |        | "        | "         | "   | "            | "                 |         |         |             | 5.85                             |                                        |                                                    |
| 22    | 150    | "        | "         | "   | "            | "                 |         |         |             | 5.08                             |                                        |                                                    |
| 23    |        | "        | "         | "   | "            | "                 |         |         |             | 5.69                             |                                        |                                                    |
| 24    |        | "        | "         | "   | "            | "                 |         |         |             | 4.78                             |                                        |                                                    |
| 25    |        | "        | "         | "   | "            | "                 |         |         |             | 4.45                             |                                        |                                                    |
| 26    | 149    | "        | "         | "   | "            | "                 |         | 10      |             | 4.50                             |                                        |                                                    |
| 27    |        | "        | "         | "   | "            | "                 |         | 10      |             | 3.64                             |                                        |                                                    |
| 28    |        | "        | "         | "   | "            | "                 |         | 10      | 143         | 2.41                             |                                        |                                                    |
| 29    | 151    | "        | "         | "   | "            | "                 |         | 10      |             | 1.36                             |                                        |                                                    |
| 30    |        | "        | "         | "   | "            | "                 |         | 10      |             | 1.40                             |                                        |                                                    |
| 7/1   |        | "        | "         | "   | "            | "                 |         | 10      |             | 1.52                             |                                        |                                                    |
| 2     |        | "        | "         | "   | "            | "                 |         | 10      |             | 1.96                             |                                        |                                                    |
| 3     | 150½   | "        | "         | "   | "            | "                 |         | 20      |             | 1.75                             |                                        |                                                    |
| 4     |        | "        | "         | "   | "            | "                 |         | 20      |             | 1.71                             |                                        |                                                    |
| 5     |        | "        | "         | "   | "            | "                 |         | 20      |             | 1.63                             |                                        |                                                    |
| 6     | 147    | "        | "         | "   | "            | "                 |         | 20      | 131         | 1.10                             |                                        |                                                    |
| 7     |        | "        | "         | "   | "            | "                 |         | 20      |             | 1.07                             |                                        |                                                    |
| 8     |        | "        | "         | "   | "            | "                 |         | 20      |             | 1.27                             |                                        |                                                    |
| 9     | 147    | 1150     | 50        | 50  | 125          | 165               |         | 20      |             | 0.91                             |                                        |                                                    |
| 10    |        | "        | "         | "   | "            | "                 |         | 20      | 118         | 0.99                             |                                        |                                                    |
| 11    |        | "        | "         | "   | "            | "                 |         | 20      |             | 1.09                             |                                        |                                                    |
| 12    |        | "        | "         | "   | "            | "                 |         | 20      |             | 0                                |                                        |                                                    |
| 13    | 145½   | "        | "         | "   | "            | "                 |         | 20      |             | 0                                |                                        |                                                    |
| 14    |        | "        | "         | "   | "            | "                 |         | 20      | 121         | 0                                |                                        |                                                    |
| 15    |        | "        | "         | "   | "            | "                 |         | 20      |             | 0                                |                                        |                                                    |
| 16    | 145    | 1250     | 50        | 50  | 150          | 180               |         | 20      |             | 0                                |                                        |                                                    |
| 17    |        | "        | "         | "   | "            | "                 |         | 20      | 132         | 0                                |                                        |                                                    |
| 18    |        | "        | "         | "   | "            | "                 |         | 20      |             | 0                                |                                        |                                                    |
| 19    |        | "        | "         | "   | "            | "                 |         | 20      |             | 0                                |                                        |                                                    |
| 20    | 146½   | "        | "         | "   | "            | "                 |         | 20      |             | 0                                |                                        |                                                    |
| 21    |        | "        | "         | "   | "            | "                 |         | 20      |             | 0                                |                                        |                                                    |
| 22    |        | "        | "         | "   | "            | "                 |         | 20      | 134         | 0                                |                                        |                                                    |
| 23    |        | 1350     | 50        | 40  | 175          | 205               |         | 20      |             | 0                                |                                        |                                                    |
| 24    | 147    | "        | "         | "   | "            | "                 |         |         |             | 0                                |                                        |                                                    |
| 25    |        | "        | "         | "   | "            | "                 |         |         |             | 0                                |                                        |                                                    |
| 26    | 146½   | "        | "         | "   | "            | "                 |         |         |             | 0                                |                                        |                                                    |
| 7/27  |        |          |           |     |              |                   |         |         | 114         | 0                                |                                        |                                                    |
| 28    |        |          |           |     |              |                   |         |         |             | 0                                |                                        |                                                    |
| 29    |        |          | Full Diet |     |              |                   |         |         |             |                                  |                                        | Patient Discharged                                 |
| 8/7   | 152½   |          | Full Diet |     |              |                   |         |         | 154         | 0                                |                                        | Follow-up in O.P.D.<br>All weights with<br>clothes |
| 13    | 153½   |          | Full Diet |     |              |                   |         |         | 138         | 0                                |                                        |                                                    |
| 21    | 155½   |          | Full Diet |     |              |                   |         |         | 124         | 0                                |                                        |                                                    |
| 28    | 154½   |          | Full Diet |     |              |                   |         |         | 129         |                                  |                                        |                                                    |
| 10/4  | 154½   |          | Full Diet |     |              |                   |         |         | 149         | 0                                |                                        |                                                    |
| 16/8  | 162    |          | Full Diet |     |              |                   |         |         | 149         | 0                                |                                        |                                                    |
| 20    | 157    |          | Full Diet |     |              |                   |         |         | 127         | 0                                |                                        |                                                    |
| 11/19 | 162    |          | Full Diet |     |              |                   |         |         | 111         | 0                                |                                        |                                                    |
| 12/17 | 159½   |          | Full Diet |     |              |                   |         |         | 128         | 0                                |                                        |                                                    |
| 1935  |        |          |           |     |              |                   |         |         |             |                                  |                                        |                                                    |
| 1/1   |        |          | Full Diet |     |              |                   |         |         | 140         | 0                                |                                        |                                                    |
| 2/11  | 165½   |          | Full Diet |     |              |                   |         |         | 142         | 0                                |                                        |                                                    |
| 3/16  | 163½   |          | Full Diet |     |              |                   |         |         | 121         | 0                                |                                        |                                                    |



| DATE  | WEIGHT | CALORIES     | PROTEIN | FAT | CARBOHYDRATE | AVAILABLE GLUCOSE | INSULIN | VITAMIN | BLOOD SUGAR | GMS. URINE SUGAR<br>PER 24 HOURS | CASE NO. 2—I. G.<br>Hospital No. 50103<br><br>REMARKS                                           |
|-------|--------|--------------|---------|-----|--------------|-------------------|---------|---------|-------------|----------------------------------|-------------------------------------------------------------------------------------------------|
| 1934  |        |              |         |     |              |                   |         |         |             |                                  |                                                                                                 |
| 10/15 | 184½   | 1615         | 60      | 75  | 175          | 210               |         |         |             | 17.1                             |                                                                                                 |
| 16    | 184¼   | "            | "       | "   | "            | "                 |         |         | 178         | 0                                |                                                                                                 |
| 17    | 182¼   | "            | "       | "   | "            | "                 |         |         |             | 0                                |                                                                                                 |
| 18    | 182    | "            | "       | "   | "            | "                 |         |         | 144         | 0                                |                                                                                                 |
| 19    | 179    | 1715         | 60      | 75  | 200          | 235               |         |         |             | 2.5                              |                                                                                                 |
| 20    | 179½   | "            | "       | "   | "            | "                 |         |         | 144         | 6.2                              |                                                                                                 |
| 21    | 180½   | "            | "       | "   | "            | "                 |         |         |             | 0                                |                                                                                                 |
| 22    | 180¼   | "            | "       | "   | "            | "                 |         |         | 148         | 4.95                             |                                                                                                 |
| 23    | 179½   | 1815         | 60      | 75  | 225          | 260               |         |         |             | 3.12                             |                                                                                                 |
| 24    | 178¾   | "            | "       | "   | "            | "                 |         |         | 130         | 4.25                             |                                                                                                 |
| 25    | 178½   | "            | "       | "   | "            | "                 |         |         |             | 4.6                              |                                                                                                 |
| 26    | 179    | "            | "       | "   | "            | "                 |         |         | 137         | 3.82                             |                                                                                                 |
| 27    | 179    | 1875         | 75      | 75  | 225          | 267               |         |         |             | 4.5                              |                                                                                                 |
| 28    | 179    | "            | "       | "   | "            | "                 |         |         |             | 6.7                              |                                                                                                 |
| 29    | 177¾   | "            | "       | "   | "            | "                 |         | 6       | 130         | 0                                |                                                                                                 |
| 30    | 178    | "            | "       | "   | "            | "                 |         | 6       |             | 0                                |                                                                                                 |
| 31    | 178    | "            | "       | "   | "            | "                 |         | 6       | 128         | 0                                |                                                                                                 |
| 11/1  | 177¾   | "            | "       | "   | "            | "                 |         | 6       |             | 0                                |                                                                                                 |
| 2     | 175½   | "            | "       | "   | "            | "                 |         | 6       | 134         | 4.5                              |                                                                                                 |
| 3     | 175½   | 2075         | 75      | 75  | 275          | 317               |         | 10      |             | 0                                |                                                                                                 |
| 4     | 177¼   | "            | "       | "   | "            | "                 |         | 10      |             | 0                                |                                                                                                 |
| 5     | 176    | "            | "       | "   | "            | "                 |         | 10      | 139         | 0                                |                                                                                                 |
| 6     | 176    | "            | "       | "   | "            | "                 |         | 10      |             | 0                                |                                                                                                 |
| 7     | 176    | "            | "       | "   | "            | "                 |         | 10      | 138         | 0                                |                                                                                                 |
| 8     | 175¼   | "            | "       | "   | "            | "                 |         | 10      |             | 0                                |                                                                                                 |
| 9     | 175¾   | 2275         | 75      | 75  | 325          | 367               |         | 10      | 141         | 2.8                              |                                                                                                 |
| 10    | 177¼   | "            | "       | "   | "            | "                 |         | 10      |             | 0                                |                                                                                                 |
| 11    | 175¼   | "            | "       | "   | "            | "                 |         | 10      |             | 0                                |                                                                                                 |
| 12    | 177    | "            | "       | "   | "            | "                 |         | 10      | 133         | 0                                |                                                                                                 |
| 13    | 175¼   | "            | "       | "   | "            | "                 |         | 10      |             | 0                                |                                                                                                 |
| 14    | 174½   | "            | "       | "   | "            | "                 |         | 10      | 127         | 0                                | Furuncle right knee                                                                             |
| 15    | 176¼   | "            | "       | "   | "            | "                 |         | 10      |             | 0                                |                                                                                                 |
| 16    | 175¾   | "            | "       | "   | "            | "                 |         | 10      | 142         | 0                                |                                                                                                 |
| 17    | 175    | "            | "       | "   | "            | "                 |         | 10      |             | 0                                |                                                                                                 |
| 18    | 175    | "            | "       | "   | "            | "                 |         | 10      |             | 0                                |                                                                                                 |
| 19    | 175    | "            | "       | "   | "            | "                 |         | 10      | 143         | 0                                |                                                                                                 |
| 20    | 175    | "            | "       | "   | "            | "                 |         | 10      |             | 0                                |                                                                                                 |
| 21    | 175    | "            | "       | "   | "            | "                 |         | 10      | 137         | 0                                |                                                                                                 |
| 22    | 174¼   | "            | "       | "   | "            | "                 |         | 10      |             | 6.6                              |                                                                                                 |
| 23    | 174¼   | "            | "       | "   | "            | "                 |         | 10      | 137         | 0                                | Drowsy from 5 to 7 P. M.                                                                        |
| 24    | 173¾   | "            | "       | "   | "            | "                 |         | 10      |             | 0                                |                                                                                                 |
| 25    | 172¼   | "            | "       | "   | "            | "                 |         | 10      |             | 0                                |                                                                                                 |
| 26    | 173    | "            | "       | "   | "            | "                 |         | 10      | 128         | 0                                |                                                                                                 |
| 27    | 173¼   | "            | "       | "   | "            | "                 |         |         |             | 0                                |                                                                                                 |
| 28    | 172¼   | "            | "       | "   | "            | "                 |         |         | 123         | 0                                |                                                                                                 |
| 12/10 | 190½   | Special Diet |         |     |              |                   |         |         | 132         | 0                                | Follow-up in O.P.D.<br>All weights with<br>clothes<br>Home diet similar to<br>diet on discharge |
| 12/22 | 187¼   | Special Diet |         |     |              |                   |         |         | 182         | +                                |                                                                                                 |
| 1935  |        |              |         |     |              |                   |         |         |             |                                  |                                                                                                 |
| 1/7   | 188½   | Special Diet |         |     |              |                   |         |         | 138         | 0                                |                                                                                                 |
| 25    | 187½   | Special Diet |         |     |              |                   |         |         | 133         | +                                |                                                                                                 |
| 2/18  | 188    | Special Diet |         |     |              |                   |         |         | 139         | +                                |                                                                                                 |
| 3/11  | 189½   | Special Diet |         |     |              |                   |         |         | 135         | +                                |                                                                                                 |
| 30    | 189½   | Special Diet |         |     |              |                   |         |         | 148         | 7.0                              |                                                                                                 |
| 4/16  | 187½   | Special Diet |         |     |              |                   |         |         | 121         | 0                                |                                                                                                 |
| 4/30  | 189    | Special Diet |         |     |              |                   |         |         | 160         | 0                                |                                                                                                 |

crystalline vitamin B<sub>1</sub> to these tissues acts as a catalyst in the lactate pyrophosphate system.

#### ORIGINAL EXPERIMENTS

In the spring of 1934, the chemical studies of Williams, Waterman and others opened the way to clinical investigation of the relationship of vitamin B<sub>1</sub> to the carbohydrate metabolism by placing large amounts of crystalline vitamin B<sub>1</sub> at our disposal. It became pos-

sible to study the effects of the pure antineuritic component of the old vitamin B complex.

A group of eleven cases, proven diabetics according to present standards, was selected for study. There were ten adults, five males and five females, and one child, in various stages of the disease. All of these patients were hospitalized for a period of control observation and when they were as well stabilized as

possible the oral administration of vitamin B<sub>1</sub> was begun. The usual daily dosage was ten mgms., continued for twenty-eight consecutive days. Toward the end of this period, a highly potent concentrate of known B<sub>1</sub> content, proven by biological assay, was substituted in some of the cases for purposes of economy. The patients were kept under observation for some time after the administration of the vitamin was stopped, at first, in the hospital and, subsequently, by fol-

low-up study. Detailed reports of the individual cases follow.

increase in the utilization of carbohydrates was lost as soon as administration of the B<sub>1</sub> was stopped. Case III maintained the gain for two months after cessation of the vitamin. An increased utilization is still in evidence in case II (after five months) and in case I (after ten months). In case VI, there was a diminished intake of insulin while the vitamin was given and an increased utilization of carbohydrates thereafter during a follow-up period of six months.

| DATE  | WEIGHT | CALORIES | PROTEIN | FAT | CARBOHYDRATE | AVAILABLE GLUCOSE | INSULIN | VITAMIN | BLOOD SUGAR | GMS. URINE SUGAR PER 24 HOURS | REMARKS                                   |
|-------|--------|----------|---------|-----|--------------|-------------------|---------|---------|-------------|-------------------------------|-------------------------------------------|
| 1934  |        |          |         |     |              |                   |         |         |             |                               | CASE NO. 3—M. I.<br>Hospital No. 50152    |
| 10/18 | 171    | 1615     | 60      | 75  | 175          | 210               |         |         | 405         | 18.2                          |                                           |
| 19    | 169½   | "        | "       | "   | "            | "                 | 20      |         |             | 5.0                           |                                           |
| 20    | 169½   | "        | "       | "   | "            | "                 | 20      |         | 210         | 3.6                           |                                           |
| 21    | 169½   | "        | "       | "   | "            | "                 | 20      |         |             | 0                             |                                           |
| 22    | 168½   | "        | "       | "   | "            | "                 | 20      |         | 218         | 0                             |                                           |
| 23    | 168½   | "        | "       | "   | "            | "                 | 10      |         |             | 0                             |                                           |
| 24    | 168    | "        | "       | "   | "            | "                 | 10      |         | 186         | 2.3                           |                                           |
| 25    | 167½   | "        | "       | "   | "            | "                 | 5       |         |             | 3.6                           |                                           |
| 26    | 167    | "        | "       | "   | "            | "                 | 5       |         | 186         | 1.8                           |                                           |
| 27    | 167½   | "        | "       | "   | "            | "                 | 5       |         |             | 4.6                           |                                           |
| 28    | 166½   | "        | "       | "   | "            | "                 | 5       |         |             | 6.2                           |                                           |
| 29    | 165½   | "        | "       | "   | "            | "                 | 5       |         | 236         | 4.5                           |                                           |
| 30    | 167½   | "        | "       | "   | "            | "                 | 5       | 6       |             | 0.75                          |                                           |
| 31    | 167½   | "        | "       | "   | "            | "                 | 5       | 6       | 190         | 0                             | Pain in legs disappeared                  |
| 11/1  | 167½   | "        | "       | "   | "            | "                 | 5       | 6       |             | 4.6                           | Slight pain in legs                       |
| 2     | 167½   | "        | "       | "   | "            | "                 | 5       | 6       | 224         | 3.8                           |                                           |
| 3     | 167    | "        | "       | "   | "            | "                 | 5       | 10      |             | 5.5                           |                                           |
| 4     | 166½   | "        | "       | "   | "            | "                 | 5       | 10      |             | 3.2                           |                                           |
| 5     | 167    | "        | "       | "   | "            | "                 | 5       | 10      | 202         | 3.8                           |                                           |
| 6     | 167½   | "        | "       | "   | "            | "                 | 5       | 10      |             | 4.2                           |                                           |
| 7     | 167    | "        | "       | "   | "            | "                 | 5       | 10      | 184         | 3.4                           |                                           |
| 8     | 166    | "        | "       | "   | "            | "                 | 5       | 10      |             | 2.7                           |                                           |
| 9     | 166½   | "        | "       | "   | "            | "                 | 5       | 10      | 182         | 4.2                           |                                           |
| 10    | 165    | "        | "       | "   | "            | "                 | 5       | 10      |             | 1.7                           |                                           |
| 11    | 165½   | "        | "       | "   | "            | "                 | 5       | 10      |             | 3.75                          |                                           |
| 12    | 166    | "        | "       | "   | "            | "                 | 5       | 10      | 192         | 5.2                           | Several attacks of dizziness and weakness |
| 13    | 165½   | "        | "       | "   | "            | "                 | 5       | 10      |             | 2.9                           |                                           |
| 14    | 165½   | "        | "       | "   | "            | "                 | 5       | 10      | 224         | 3.3                           |                                           |
| 15    | 166    | "        | "       | "   | "            | "                 | 5       | 10      |             | 3.6                           |                                           |
| 16    | 165½   | "        | "       | "   | "            | "                 | 5       | 10      | 186         | 2.5                           |                                           |
| 17    | 164½   | "        | "       | "   | "            | "                 |         | 10      |             | 0                             |                                           |
| 18    | 164½   | "        | "       | "   | "            | "                 |         | 10      |             | 3.6                           |                                           |
| 19    | 164½   | "        | "       | "   | "            | "                 |         | 10      | 180         | 2.9                           |                                           |
| 20    | 164    | "        | "       | "   | "            | "                 |         | 10      |             | 0                             |                                           |
| 21    | 164½   | "        | "       | "   | "            | "                 |         | 10      | 180         | 3.1                           |                                           |
| 22    | 164½   | "        | "       | "   | "            | "                 |         | 10      |             | 4.9                           |                                           |
| 23    | 164    | "        | "       | "   | "            | "                 |         | 10      | 174         | 0                             |                                           |
| 24    | 164    | "        | "       | "   | "            | "                 |         | 10      |             | 3.2                           |                                           |
| 25    | 163½   | "        | "       | "   | "            | "                 |         | 10      |             | 3.3                           |                                           |
| 26    | 162    | "        | "       | "   | "            | "                 |         | 10      | 150         |                               | Left hospital against advice              |

low-up study. Detailed reports of the individual cases follow.

## RESULTS

It will be observed that six of the eleven cases (I, II, III, IV, V, VI) showed increased carbohydrate utilization of varying degree during the period of administration of the vitamin, as evidenced by the diminished blood sugar and urinary sugar. The remaining five cases (VII, VIII, IX, X, XI) failed to present any such phenomena, either during the administration of the vitamin or thereafter.

In two of the six favorable cases (IV and V), the

Since discontinuing the vitamin, the insulin requirement in this case has risen but not to the previous level.

One of the cases (III) showing an accelerated carbohydrate utilization died, subsequently, of uremia. Post mortem examination of the pancreas showed fatty infiltration and interstitial fibrosis.

Every student of diabetes understands the necessity for careful consideration of the effects of dietary restriction on the clinical course of this condition. This factor must be borne in mind in evaluating the results of the study presented herewith.

## PROTOCOLS

Case No. I: L. D., hospital No. 48362, colored male, age 37, a known diabetic for three years. Admitted to the hospital June 7, 1934, complaining of polyuria, polydipsia, loss of ten pounds during the last eight months, weakness, pruritus. He was treated by diet, without insulin. There was no history of diabetes in the family. The patient was born in the British West Indies but has lived in the United States for the past seventeen years.

*Physical examination* revealed a well developed, fairly well nourished patient. Except for large tonsils and some cervical adenopathy, no abnormal findings were noted.

*Laboratory findings:* Wassermann negative; hemoglobin 85%, r. b. e. 5,760,000, w. b. e. 4,600, normal differential; urea nitrogen 11.8 mgm.; creatinine 1.6 mgm.; cholesterol 216 mgm. The electrocardiograph was normal except for slight left axis deviation.

*Analysis*—This patient was stabilized readily. Within 48 hours after the vitamin was begun there was a noticeable and progressive drop in the blood sugar and urinary sugar. On the 7th day the vitamin was doubled. There was no change in the rate of decline. On the 17th day, the urine was free of sugar. Increasing the diet by 25 gms. of carbohydrate had no effect. After 27 days the vitamin was discontinued. Diet was increased up to full diet. There was a loss of 2 pounds during the administration of the vitamin. Patient was followed for 10 months after discharge on a full diet and without vitamin. During these 10 months he gained 17 pounds in weight, and at last observation the blood sugar was normal and the urine was free of sugar.

Case No. II: I. G., hospital No. 50105, white male, age 47, a known diabetic for two years. He was treated with insulin originally for a short time and was an active patient in the out-patient department, diabetic clinic, where he was treated by diet alone. Admitted to the hospital October 15, 1934, complaining of weakness and pain in the lower extremities, loss of fifteen pounds in the past four months, and general fatigue. There was no history of diabetes in the family.

*Physical examination* revealed a well nourished patient. The positive findings were emphysematous chest, slight cardiac enlargement, moderate thickening of the peripheral arteries and a smooth palpable liver one and one-half fingers' breadth below the costal margin. The osellometric readings showed a diminished pulsation equally in both legs.

*Laboratory findings:* Wassermann negative; hemoglobin 95%, r. b. c. 5,152,000, w. b. c. 11,200, normal differential; urea nitrogen 16.6 mgm. creatinine 1.6 mgm. The electrocardiograph was normal except for low voltage.

*Analysis*—This patient became sugar free spontaneously. The diet was then increased by adding 50 gms. of carbohydrate. Following this, for 7 days he seemed fairly well stabilized. 15 gms. of protein were added. On the 14th day after admission the vitamin was started, in 6 mgm. doses for 4 days, and thereafter in 10 mgm. doses for 24 days. Immediately after starting the vitamin, the urine became free of sugar, and remained so except for 3 isolated days. The blood sugar varied slightly between 127 and 143. There was a loss of 6 pounds while taking the vitamin.

Patient has been followed for 5 months in the O. P. D. during which time his weight has been constant. There was a slight rise in the blood sugar four weeks after discharge, but thereafter blood sugar levels were comparable to that observed during his hospital period. At the last observation the blood sugar had risen to 160.

Case No. III: M. I., hospital No. 50152, white male, age 60, a known diabetic for over six years. He was treated with insulin constantly for the past three and a half years, taking about twenty units daily for the past five months. Admitted to the hospital October 18, 1934, complaining of severe pains in both legs and feet, numbness and tingling of the feet and toes, swelling of the ankles at night, morning cough, dyspnoea on moderate exertion, polyuria, dysuria and impaired vision. There was no history of diabetes in the family.

*Physical examination* revealed a sallow complexioned, obese, elderly patient, appearing older than stated age. The positive findings were bilateral *arcus senilis*, teeth missing, coated tongue, emphysematous lungs, enlarged heart with sounds of poor quality, A<sub>2</sub> loud and ringing, blood pressure 176/106, enlarged firm prostate, tortuous hardened arteries, and pitting oedema of both lower extremities. The osellometric readings showed diminished pulsation, more marked in the left leg.

*Laboratory findings:* Wassermann negative; hemoglobin 65%, r. b. e. 4,000,000, w. b. e. 8,200, normal differential; urea nitrogen 43. mgm.; creatinine 3.3 mgm.; uric acid 5.1 mgm.; sedimentation time 42 mm. in 45 minutes. The electrocardiograph showed left axis deviation and noticeable Q.R.S.

Case No. III: M. I., readmitted to the hospital February 27, 1935, complaining of weakness, attacks of dizziness and syncope, cramp like pains in legs and loss of thirty pounds in the past two months.

*Physical examination* disclosed evidence of impending uremia and advanced arteriosclerosis.

*Laboratory findings:* Urine showed albumin ++, sugar — trace; urea nitrogen 57.6 mgm.; creatinine 5.6 mgm.; sugar 210 mgm.; uric acid 6.2 mgm.; cholesterol 230 mgm. Death was due to uremia—March 9, 1935.

Only the body and tail of the pancreas were secured for *pathologic examination*. There was a large amount of fatty infiltration and a moderate degree of interstitial fibrosis.

Islets of Langerhans are seen microscopically; they have a somewhat disintegrated appearance, but are not greatly fibrosed. There is cystic dilatation of some of the ducts.

*Analysis*—This patient was stabilized only by reducing his insulin. On the 11th day, the blood sugar began to increase. The following day the vitamin was started, in 6 mgm. doses for 4 days, and then for 24 days in 10 mgm. daily doses. The urine sugar declined shortly after the administration of the vitamin, and thereafter fluctuated between 0 and 5½ gms. The blood sugar showed an irregular decline which was more marked after the 5 units of insulin was discontinued on 11/16/34. At the conclusion of the study, the blood sugar was 150 which was less than one-half of the level before beginning the vitamin, even though 5 units of insulin were being administered at that time.

The patient left against advice, and when re-admitted three months later in uremia, his blood sugar was 210, although he had had no insulin nor dietary supervision during those three months.

Case No. IV: J. K., hospital No. 50169, white male, age 52, a known diabetic for two years. Active in the out-patient department, diabetic clinic where he was treated by diet alone. Admitted to the hospital October 18, 1934, complaining of intermittent precordial pain, severe in nature, radiating up to the left shoulder, aggravated by exercise, dyspnoea, weakness and pains in both legs. One son died of diabetes.

*Physical examination* revealed a well nourished patient. The positive findings were cardiac enlargement to the left, sounds of fair quality, A<sub>2</sub> accentuated, blood pressure 130/74, liver one finger's breadth below the costal margin,

| DATE  | WEIGHT            | CALORIES | PROTEIN      | FAT | CARBOHYDRATE | AVAILABLE GLUCOSE | INSULIN | VITAMIN | BLOOD SUGAR     | GMS. URINE SUGAR PER 21 HOURS | CASE NO. 4—J. K.<br>Hospital No. 59169     |
|-------|-------------------|----------|--------------|-----|--------------|-------------------|---------|---------|-----------------|-------------------------------|--------------------------------------------|
|       |                   |          |              |     |              |                   |         |         |                 |                               | REMARKS                                    |
| 1934  |                   |          |              |     |              |                   |         |         |                 |                               |                                            |
| 10/18 | 138 $\frac{1}{2}$ | 1615     | 60           | 75  | 175          | 210               |         |         |                 |                               |                                            |
| 19    | 138 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         | 240             | 16.0                          |                                            |
| 20    | 137 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         |                 | 5.7                           |                                            |
| 21    | 137 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         |                 | 9.8                           |                                            |
| 22    | 138               | "        | "            | "   | "            | "                 |         |         | 182             | 8.2                           |                                            |
| 23    | 137 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         |                 | 4.5                           |                                            |
| 24    | 136 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         | 164             | 3.9                           |                                            |
| 25    | 136 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         |                 | 7.4                           |                                            |
| 26    | 135 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         | 168             | 5.6                           |                                            |
| 27    | 135 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         |                 | 17.2                          |                                            |
| 28    | 135 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         |                 | 12.4                          |                                            |
| 29    | 135 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         | 156             | 3.8                           |                                            |
| 30    | 135               | "        | "            | "   | "            | "                 |         |         |                 | 2.5                           |                                            |
| 31    | 135 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         | 170             | 0                             |                                            |
| 11/1  | 136 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         |                 | 4.9                           |                                            |
| 2     | 134 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         | 15 <sup>a</sup> | 2.4                           |                                            |
| 3     | 135 $\frac{1}{2}$ | 1775     | 75           | 75  | 200          | 242               |         |         |                 | 0                             |                                            |
| 4     | 135 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         |                 | 1.6                           |                                            |
| 5     | 135               | "        | "            | "   | "            | "                 |         |         | 154             | 0                             |                                            |
| 6     | 134 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         |         |                 | 7.2                           |                                            |
| 7     | 133 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      | 136             | 3.6                           |                                            |
| 8     | 134 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      |                 | 8.0                           |                                            |
| 9     | 133 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      | 158             | 4.8                           |                                            |
| 10    | 134               | "        | "            | "   | "            | "                 |         | 10      |                 | 0                             |                                            |
| 11    | 135 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      |                 | 0                             |                                            |
| 12    | 134 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      | 152             | 4.6                           |                                            |
| 13    | 134 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      |                 | 0                             |                                            |
| 14    | 134               | "        | "            | "   | "            | "                 |         | 10      | 160             | 0                             | Paresthesia of right foot                  |
| 15    | 133 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      |                 | 3.2                           |                                            |
| 16    | 133 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      | 165             | 0                             |                                            |
| 17    | 133 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      |                 | 0                             |                                            |
| 18    | 133 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      |                 | 0                             |                                            |
| 19    | 133 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      | 160             | 0                             |                                            |
| 20    | 133 $\frac{1}{2}$ | 1875     | 75           | 75  | 225          | 265               |         | 10      |                 | 0                             |                                            |
| 21    | 134 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      | 158             | 0                             |                                            |
| 22    | 134               | "        | "            | "   | "            | "                 |         | 10      |                 | 0                             |                                            |
| 23    | 134               | "        | "            | "   | "            | "                 |         | 10      | 154             | 2.6                           |                                            |
| 24    | 134 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      |                 | 0                             |                                            |
| 25    | 134 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      |                 | 0                             |                                            |
| 26    | 133 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      | 172             | 5.6                           |                                            |
| 27    | 132 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      |                 | 0                             |                                            |
| 28    | 132 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      | 170             | 0                             |                                            |
| 29    | 132 $\frac{1}{2}$ | "        | "            | "   | "            | "                 |         | 10      |                 | 4.6                           | Acute coronary closure. Study discontinued |
| 1935  |                   |          |              |     |              |                   |         |         |                 |                               |                                            |
| 1/22  | 141 $\frac{1}{2}$ |          | Special Diet |     |              |                   |         |         | 216             | +                             | Follow-up in O.P.D.                        |
| 2/6   | 137 $\frac{1}{2}$ |          | Special Diet |     |              |                   |         |         | 261             | +                             | All weights with clothes                   |
| 18    | 142               |          | Special Diet |     |              |                   |         |         | 242             | +                             | Home diet similar to diet on discharge     |
| 3/4   | 142 $\frac{1}{2}$ |          | Special Diet |     |              |                   |         |         | 256             | +                             |                                            |
| 19    | 144               |          | Special Diet |     |              |                   |         |         | 270             | +                             |                                            |
| 4/2   | 141               |          | Special Diet |     |              |                   |         |         | 294             | 67.0                          |                                            |
| 16    | 141 $\frac{1}{2}$ |          | Special Diet |     |              |                   |         |         | 314             | 30.0                          |                                            |
| 29    |                   |          | Special Diet |     |              |                   |         |         | 266             | 67.0                          |                                            |

absent pulsations in popliteal, posterior tibial and dorsalis pedis arteries on both sides. The osillometric readings showed markedly diminished pulsation in both lower extremities.

**Laboratory findings:** Wassermann negative; hemoglobin 90%, r. b. c. 5,280,000, w. b. c. 10,400, normal differential; urea nitrogen 15.4 mgm.; creatinine 1.5 mgm.; sedimentation time 17 mm. in 45 minutes. The electrocardiograph showed notched P<sub>1</sub> and P<sub>2</sub>, inverted P<sub>1</sub>, notched Q.R.S., low T, left axis deviation.

On the forty-third day of the study, the patient had an attack of acute coronary closure with typical pain, fall in blood pressure, friction rub and positive electrocardio-

graph. He remained in the hospital for six weeks and made a satisfactory recovery.

The patient was discharged January 15, 1935, weighing 134 pounds. Blood sugar 168 mgm., urine no sugar.

**Analysis**—This patient was not well stabilized. After 19 days of preliminary study and after an increase of 160 calories in his diet the vitamin was begun on November 7th. Within 3 days the sugar disappeared from the urine and remained absent except for 5 isolated days. The blood sugar increased slightly, fluctuating between 137 and 170. During the course of the vitamin administration the diet was increased by 25

gms. of carbohydrate, with little effect on the blood or urinary sugar. There was a loss of 2½ pounds during the period of vitamin administration.

On the 22nd day after the administration of the vitamin, the study was discontinued because of the occurrence of an acute coronary closure. During the

polyuria of six months duration, a loss of ten pounds in the last six months, generalized pruritus. She had been receiving ten units of insulin daily. There was no history of diabetes in the family.

Physical examination revealed a well nourished patient. No abnormal findings were noted.

| DATE | WEIGHT | CALORIES | PROTEIN      | FAT | CARBOHYDRATE | AVAILABLE GLUCOSE | INSULIN | VITAMIN | BLOOD SUGAR | GMS. URINE SUGAR PER 24 HOURS | REMARKS                  |
|------|--------|----------|--------------|-----|--------------|-------------------|---------|---------|-------------|-------------------------------|--------------------------|
| 1935 |        |          |              |     |              |                   |         |         |             |                               |                          |
| 2/4  |        | 1875     | 75           | 75  | 225          | 267               |         |         |             | 76.0                          |                          |
| 5    | 202    | "        | "            | "   | "            | "                 |         |         | 286         | 68.0                          |                          |
| 6    | 202½   | "        | "            | "   | "            | "                 |         |         |             | 60.0                          |                          |
| 7    | 202½   | "        | "            | "   | "            | "                 |         |         |             | 115.5                         |                          |
| 8    | 202½   | "        | "            | "   | "            | "                 |         |         | 274         | 75.0                          |                          |
| 9    | 203¼   | "        | "            | "   | "            | "                 |         |         |             | 91.0                          |                          |
| 10   | 202½   | "        | "            | "   | "            | "                 |         |         |             | 51.9                          |                          |
| 11   | 202½   | "        | "            | "   | "            | "                 |         |         | 244         | 70.0                          |                          |
| 12   | 203½   | "        | "            | "   | "            | "                 |         |         |             | 80.0                          |                          |
| 13   | 203½   | "        | "            | "   | "            | "                 |         |         | 216         | 62.7                          |                          |
| 14   | 202    | "        | "            | "   | "            | "                 |         |         |             | 56.0                          |                          |
| 15   | 202½   | "        | "            | "   | "            | "                 |         |         | 212         | 65.0                          |                          |
| 16   | 202½   | "        | "            | "   | "            | "                 |         | 10      |             | 40.0                          |                          |
| 17   | 202½   | "        | "            | "   | "            | "                 |         | 10      |             | 38.8                          |                          |
| 18   | 203    | "        | "            | "   | "            | "                 |         | 10      | 192         | 21.0                          |                          |
| 19   | 203    | "        | "            | "   | "            | "                 |         | 10      |             | 26.0                          |                          |
| 20   | 202½   | "        | "            | "   | "            | "                 |         | 10      | 178         | 19.5                          |                          |
| 21   | 200½   | "        | "            | "   | "            | "                 |         | 10      |             | 14.5                          |                          |
| 22   | 200½   | "        | "            | "   | "            | "                 |         | 10      |             | 26.0                          |                          |
| 23   | 200½   | "        | "            | "   | "            | "                 |         | 10      | 200         | 27.0                          |                          |
| 24   | 200½   | "        | "            | "   | "            | "                 |         | 10      |             | 21.0                          |                          |
| 25   | 200¼   | "        | "            | "   | "            | "                 |         | 10      | 196         | 29.7                          |                          |
| 26   | 200¼   | "        | "            | "   | "            | "                 |         | 10      |             | 33.0                          |                          |
| 27   | 200    | "        | "            | "   | "            | "                 |         | 10      | 182         | 33.0                          |                          |
| 28   | 200    | "        | "            | "   | "            | "                 |         | 10      |             | 46.5                          |                          |
| 3/1  | 199½   | "        | "            | "   | "            | "                 |         | 10      | 190         | 32.5                          |                          |
| 2    | 199½   | "        | "            | "   | "            | "                 |         | 20      |             |                               |                          |
| 3    | 200    | "        | "            | "   | "            | "                 |         | 20      |             | 30.0                          |                          |
| 4    | 198½   | "        | "            | "   | "            | "                 |         | 20      | 194         | 32.5                          |                          |
| 5    | 199½   | "        | "            | "   | "            | "                 |         | 20      |             | 22.0                          |                          |
| 6    | 199    | "        | "            | "   | "            | "                 |         | 20      | 188         | 20.0                          |                          |
| 7    | 199½   | "        | "            | "   | "            | "                 |         | 20      |             | 70.0                          |                          |
| 8    | 198¼   | "        | "            | "   | "            | "                 |         | 20      | 194         | 44.0                          |                          |
| 9    | 196    | "        | "            | "   | "            | "                 |         | 20      |             | 17.5                          |                          |
| 10   | 195½   | "        | "            | "   | "            | "                 |         | 20      |             | 25.0                          |                          |
| 11   | 195    | "        | "            | "   | "            | "                 |         | 20      | 198         | 27.0                          |                          |
| 12   | 196¼   | "        | "            | "   | "            | "                 |         | 20      |             | 22.5                          |                          |
| 13   | 196½   | "        | "            | "   | "            | "                 |         | 20      | 194         | 15.0                          |                          |
| 14   | 197½   | "        | "            | "   | "            | "                 |         | 20      |             | 32.5                          |                          |
| 15   | 196¼   | "        | "            | "   | "            | "                 |         | 20      | 198         | 19.5                          |                          |
| 16   | 196    | "        | "            | "   | "            | "                 |         |         |             | 42.9                          |                          |
| 17   | 196    | "        | "            | "   | "            | "                 |         |         |             | 50.0                          |                          |
| 18   | 195    | "        | "            | "   | "            | "                 |         |         | 332         |                               | Patient Discharged       |
| 3/21 | 190½   |          | Special Diet |     |              |                   |         |         | 168         | +                             | Follow-up in O.P.D.      |
| 4/4  | 201½   |          | Special Diet |     |              |                   |         |         | 214         | 29.0                          | All weights with clothes |
| 4/19 | 200¼   |          | Special Diet |     |              |                   |         |         | 204         | 40.0                          |                          |
| 5/4  | 201½   |          | Special Diet |     |              |                   |         |         | 212         | 35.0                          |                          |

treatment of this cardiac disease, carbohydrates were freely given.

He was discharged on January 15, 1935, and has been followed in the O. P. D. for 3½ months. During this time he has gained 10 pounds in weight, and his blood and urinary sugars are markedly higher than during the time of the vitamin administration.

Case No. V: T. K., hospital No. 51534, white female, age 43, a known diabetic for three months. Admitted February 4, 1935, complaining of polydipsia, polyphagia and

*Laboratory findings:* Wassermann negative; hemoglobin 85%, r. b. c. 4,640,000, w. b. c. 6,800, normal differential; basal metabolism minus five; sedimentation time normal; urea nitrogen 16 mgm.; creatinine 1.5 mgm.; uric acid 4.0 mgm.; cholesterol 288 mgm. The electrocardiograph showed slurred Q.R.S.s. and left axis deviation.

*Analysis*—This patient was fairly easily stabilized. After 11 days the vitamin was begun in 10 mgm. doses. There was an immediate drop in the urinary sugar output, to about ½ of the previous level. No

| DATE  | WEIGHT | CALORIES | PROTEIN      | FAT | CARBOHYDRATE | AVAILABLE GLUCOSE | INSULIN | VITAMIN | BLOOD SUGAR | GMS. URINE SUGAR<br>PER 24 HOURS | CASE NO. 6—D. S.<br>Hospital No. 49251<br><br>REMARKS |
|-------|--------|----------|--------------|-----|--------------|-------------------|---------|---------|-------------|----------------------------------|-------------------------------------------------------|
| 1934  |        |          |              |     |              |                   |         |         |             |                                  |                                                       |
| 8/10  | 201½   | 1515     | 60           | 75  | 150          | 187               | 75      |         | 363         |                                  |                                                       |
| 11    | 197    | 1776     | 60           | 75  | 215          | 232               | 75      |         | 429         | 129.0                            |                                                       |
| 12    | 195    | "        | "            | "   | "            | "                 | 75      |         |             | 78.0                             |                                                       |
| 13    | "      | "        | "            | "   | "            | "                 | 75      |         | 417         | 78.7                             |                                                       |
| 14    | 195½   | "        | "            | "   | "            | "                 | 75      | 20      |             | 40.0                             | Hypoglycemic<br>reaction †                            |
| 15    | 195    | 1875     | 60           | 75  | 240          | 277               | 55      | 20      | 369         | 48.0                             | Hypoglycemic<br>reaction ††                           |
| 16    | 194½   | 1715     | 60           | 75  | 200          | 237               | 45      | 20      |             | 55.5                             | Hypoglycemic<br>reaction †                            |
| 17    | 193    | 1776     | 60           | 75  | 215          | 252               | 40      | 20      | 405         | 73.8                             | —                                                     |
| 18    | 193    | "        | "            | "   | "            | "                 | 40      | 20      |             | 94.4                             |                                                       |
| 19    | "      | "        | "            | "   | "            | "                 | 40      | 20      |             | 83.0                             |                                                       |
| 20    | 192    | "        | "            | "   | "            | "                 | 40      | 20      | 408         | 82.5                             |                                                       |
| 21    | 190½   | "        | "            | "   | "            | "                 | 40      | 30      |             | 51.5                             |                                                       |
| 22    | 190½   | "        | "            | "   | "            | "                 | 30      | 40      | 402         | 93.0                             | Hypoglycemic<br>reaction ††                           |
| 23    | 190½   | "        | "            | "   | "            | "                 | 30      | 40      |             | 161.7                            | Hypoglycemic<br>reaction †††                          |
| 24    | 189½   | "        | "            | "   | "            | "                 | 25      | 40      | 420         | 139.1                            |                                                       |
| 25    | 189    | "        | "            | "   | "            | "                 | 25      | 40      |             | 161.0                            |                                                       |
| 26    | 189    | "        | "            | "   | "            | "                 | 25      | 40      |             | 216.3                            |                                                       |
| 27    | 189    | "        | "            | "   | "            | "                 | 25      | 20      | 426         | 83.8                             |                                                       |
| 28    | 189    | 1937     | 60           | 93  | 215          | 254               | 25      | 50      |             | 129.5                            | Hypoglycemic<br>reaction ††                           |
| 29    | 189    | 1730     | 60           | 70  | 215          | 252               | 25      | 50      | 441         | 151.0                            |                                                       |
| 30    | 187½   | "        | "            | "   | "            | "                 | 25      | 50      |             | 128.8                            |                                                       |
| 31    | 186½   | "        | "            | "   | "            | "                 | 25      | 60      | 444         | 183.1                            |                                                       |
| 9/1   | 183½   | "        | "            | "   | "            | "                 | 25      | 60      |             | 212.0                            |                                                       |
| 2     | 186    | 1852     | "            | "   | "            | "                 | 25      | 60      |             | 150.0                            |                                                       |
| 3     | 186    | "        | 65           | 80  | 215          | 257               | 25      | 70      |             | 177.7                            |                                                       |
| 4     | 186    | "        | "            | "   | "            | "                 | 25      | 70      | 450         | 184.3                            |                                                       |
| 5     | 185½   | "        | "            | "   | "            | "                 | 25      | 70      |             | 216.2                            |                                                       |
| 6     | 185    | "        | "            | "   | "            | "                 | 25      | 80      | 393         | 134.3                            |                                                       |
| 7     | 184½   | "        | "            | "   | "            | "                 | 25      | 80      |             | 140.5                            |                                                       |
| 8     | 184½   | "        | "            | "   | "            | "                 | 25      | 80      | 417         | 191.0                            |                                                       |
| 9     | 184½   | "        | "            | "   | "            | "                 | 25      | 80      |             | 140.0                            |                                                       |
| 10    | 184½   | "        | "            | "   | "            | "                 | 25      | 90      |             | 160.0                            |                                                       |
| 11    | 181½   | "        | "            | "   | "            | "                 | 25      | 90      | 438         | 219.0                            |                                                       |
| 12    | 184½   | "        | "            | "   | "            | "                 | 25      | 90      |             | 143.4                            |                                                       |
| 13    | 181½   | "        | "            | "   | "            | "                 | 25      | 90      | 411         | 96.4                             |                                                       |
| 14    | 181½   | "        | "            | "   | "            | "                 | 25      | 90      |             | 250.0                            |                                                       |
| 15    | 184½   | "        | "            | "   | "            | "                 | 25      |         | 342         |                                  | Patient discharged                                    |
| 10/4  | 186    |          | Special Diet |     |              |                   | 40      |         |             |                                  | Follow-up at home                                     |
| 10/26 | 185    |          | Special Diet |     |              |                   | 45      |         |             |                                  |                                                       |
| 11/8  | 185½   |          | Special Diet |     |              |                   | 45      |         |             |                                  |                                                       |
| 11/10 |        |          | Special Diet |     |              |                   |         |         | 348         |                                  |                                                       |
| 11/19 | 187    |          | Special Diet |     |              |                   | 45      |         |             |                                  |                                                       |
| 11/30 | 192½   |          | Special Diet |     |              |                   | 55      |         | 175         |                                  |                                                       |
| 1935  |        |          |              |     |              |                   |         |         |             |                                  |                                                       |
| 1/18  |        |          | Special Diet |     |              |                   |         |         | 102         |                                  |                                                       |
| 2/16  | 189    |          | Special Diet |     |              |                   | 50      |         |             |                                  |                                                       |
| 3/29  | 201½   |          | Special Diet |     |              |                   | 60      |         | 135         | 0                                |                                                       |
| 4/5   |        |          | Special Diet |     |              |                   | 60      | 10      |             |                                  |                                                       |
| 6     |        |          | Special Diet |     |              |                   | 60      | 10      |             |                                  |                                                       |
| 7     |        |          | Special Diet |     |              |                   | 60      | 10      |             |                                  | Hypoglycemic<br>reaction                              |
| 8     |        |          | Special Diet |     |              |                   | 50      | 10      |             |                                  |                                                       |
| 9     |        |          | Special Diet |     |              |                   | 45      | 10      |             |                                  |                                                       |
| 10    |        |          | Special Diet |     |              |                   | 45      | 10      |             |                                  |                                                       |
| 11    |        |          | Special Diet |     |              |                   | 45      | 10      |             |                                  |                                                       |
| 12    |        |          | Special Diet |     |              |                   | 45      | 10      |             |                                  |                                                       |
| 13    |        |          | Special Diet |     |              |                   | 46      | 10      |             |                                  |                                                       |
| 14    |        |          | Special Diet |     |              |                   | 46      | 10      |             |                                  |                                                       |
| 15    | 185½   |          | Special Diet |     |              |                   | 45      | 10      | 308         | 45.0                             |                                                       |
| 27    | 185½   |          | Special Diet |     |              |                   | 45      | 10      | 175         | 0                                |                                                       |
| 28    | 191    |          | Special Diet |     |              |                   | 42      | 10      | 178         | 0                                |                                                       |
| 5/4   | 191½   |          | Special Diet |     |              |                   | 42      | 10      | 305         | 91.5                             |                                                       |



| DATE  | WEIGHT | CALORIES     | PROTEIN | FAT | CARBOHYDRATE | AVAILABLE GLUCOSE | INSULIN | VITAMIN | BLOOD SUGAR | GMS. URINE SUGAR<br>PER 24 HOURS | REMARKS                                                          |
|-------|--------|--------------|---------|-----|--------------|-------------------|---------|---------|-------------|----------------------------------|------------------------------------------------------------------|
| 1934  |        |              |         |     |              |                   |         |         |             |                                  |                                                                  |
| 10/20 | 109½   |              |         |     |              |                   |         |         |             |                                  |                                                                  |
| 21    | 109    | 1615         | 60      | 75  | 175          | 210               |         |         |             | 23.1                             |                                                                  |
| 22    | 109    | "            | "       | "   | "            | "                 |         |         | 246         | 27.5                             |                                                                  |
| 23    | 107¾   | "            | "       | "   | "            | "                 |         |         |             | 26.3                             |                                                                  |
| 24    | 107¾   | "            | "       | "   | "            | "                 |         |         | 232         | 27.2                             |                                                                  |
| 25    | 108    | "            | "       | "   | "            | "                 |         |         |             | 39.6                             |                                                                  |
| 26    | 106¾   | "            | "       | "   | "            | "                 |         |         | 232         | 45.2                             |                                                                  |
| 27    | 107½   | "            | "       | "   | "            | "                 |         | 6       |             | 18.5                             |                                                                  |
| 28    | 106¾   | "            | "       | "   | "            | "                 |         | 6       |             | 47.5                             | Chill, temp. 101.6°, pain<br>in right calf; con-<br>fined to bed |
| 29    | 105¾   | "            | "       | "   | "            | "                 |         | 6       | 226         | 78.7                             | Pain less; temp. 101°                                            |
| 30    | 104    | "            | "       | "   | "            | "                 |         | 6       |             | 115.0                            | Pain gone; temp. 99°                                             |
| 31    | 104    | "            | "       | "   | "            | "                 |         | 6       | 264         | 117.0                            |                                                                  |
| 11/1  | 104¼   | "            | "       | "   | "            | "                 |         | 6       |             | 88.0                             | Out of bed                                                       |
| 2     | 104¼   | "            | "       | "   | "            | "                 |         | 6       | 290         | 96.0                             |                                                                  |
| 3     | 104¾   | "            | "       | "   | "            | "                 |         | 10      |             | 26.8                             |                                                                  |
| 4     | 104½   | "            | "       | "   | "            | "                 |         | 10      |             | 106.0                            |                                                                  |
| 5     | 105    | "            | "       | "   | "            | "                 |         | 10      | 297         | 75.2                             |                                                                  |
| 6     | 104¾   | "            | "       | "   | "            | "                 |         | 10      |             | 99.0                             |                                                                  |
| 7     | 104¾   | "            | "       | "   | "            | "                 |         | 10      | 273         | 105.0                            |                                                                  |
| 8     | 104¾   | "            | "       | "   | "            | "                 |         | 10      |             | 82.5                             |                                                                  |
| 9     | 104½   | "            | "       | "   | "            | "                 |         | 20      | 249         | 68.7                             |                                                                  |
| 10    | 104½   | "            | "       | "   | "            | "                 |         | 20      |             | 50.0                             |                                                                  |
| 11    | 104½   | "            | "       | "   | "            | "                 |         | 20      |             | 67.5                             |                                                                  |
| 12    | 104½   | "            | "       | "   | "            | "                 |         | 20      | 248         | 78.7                             |                                                                  |
| 13    | 104½   | "            | "       | "   | "            | "                 |         | 20      |             | 114.0                            |                                                                  |
| 14    | 105    | "            | "       | "   | "            | "                 |         | 20      | 270         | 103.2                            |                                                                  |
| 15    | 103½   | "            | "       | "   | "            | "                 |         | 20      |             | 128.2                            |                                                                  |
| 16    | 104    | "            | "       | "   | "            | "                 |         | 20      | 306         | 68.2                             |                                                                  |
| 17    | 104    | "            | "       | "   | "            | "                 |         | 20      |             | 77.5                             |                                                                  |
| 18    | 103¾   | "            | "       | "   | "            | "                 |         | 20      |             | 84.0                             |                                                                  |
| 19    | 103    | "            | "       | "   | "            | "                 |         | 20      | 291         | 56.0                             |                                                                  |
| 20    | 103¼   | "            | "       | "   | "            | "                 |         | 20      |             | 63.7                             |                                                                  |
| 21    | 103½   | "            | "       | "   | "            | "                 |         | 20      | 276         | 78.0                             |                                                                  |
| 22    | 103½   | "            | "       | "   | "            | "                 |         | 20      |             | 102.9                            |                                                                  |
| 23    | 103    | "            | "       | "   | "            | "                 |         | 20      | 279         | 68.7                             |                                                                  |
| 24    | 103¼   | "            | "       | "   | "            | "                 |         | 20      |             | 51.2                             |                                                                  |
| 25    | 103    | "            | "       | "   | "            | "                 |         | 20      |             | 56.0                             |                                                                  |
| 26    | 103    | "            | "       | "   | "            | "                 |         | 20      | 279         | 55.0                             |                                                                  |
| 27    | 102¾   | "            | "       | "   | "            | "                 |         | 20      |             | 69.0                             |                                                                  |
| 28    | 102¾   | "            | "       | "   | "            | "                 |         | 20      | 244         | 42.0                             |                                                                  |
| 29    | 102    | "            | "       | "   | "            | "                 |         | 20      |             | 76.2                             |                                                                  |
| 30    | 103    | "            | "       | "   | "            | "                 |         | 20      | 258         | 62.0                             |                                                                  |
| 12/1  | 103¼   | "            | "       | "   | "            | "                 |         | 20      |             | 62.0                             |                                                                  |
| 2     | 103    | "            | "       | "   | "            | "                 |         | 20      |             | 50.4                             |                                                                  |
| 3     | 102    | "            | "       | "   | "            | "                 |         | 20      | 276         | 72.0                             |                                                                  |
| 4     | 102    | "            | "       | "   | "            | "                 |         | 20      |             | 63.0                             |                                                                  |
| 5     | 103½   | "            | "       | "   | "            | "                 |         | 20      | 264         | 52.8                             |                                                                  |
| 6     | 103    | "            | "       | "   | "            | "                 |         | 20      |             | 126.0                            |                                                                  |
| 12/7  | 102¼   | "            | "       | "   | "            | "                 |         | 20      | 242         | 42.7                             |                                                                  |
| 8     | 102¼   |              |         |     |              |                   |         |         |             |                                  |                                                                  |
| 12/22 | 106    | Special Diet |         |     |              |                   |         |         | 308         | +                                | Patient discharged                                               |
| 12/29 | 105¾   | Special Diet |         |     |              |                   |         |         | 339         | +                                | Follow-up in O.P.D.<br>All weights with clothes                  |
| 1935  |        |              |         |     |              |                   |         |         |             |                                  | Home diet similar to<br>diet on discharge                        |
| 1/5   | 105½   | Special Diet |         |     |              |                   | 20      |         | 303         | +                                |                                                                  |
| 19    | 108¼   | Special Diet |         |     |              |                   | 45      |         | 360         | +                                |                                                                  |
| 26    | 110    | Special Diet |         |     |              |                   | 45      |         | 264         | +                                |                                                                  |
| 2/2   | 110    | Special Diet |         |     |              |                   | 45      |         | 279         | +                                |                                                                  |
| 16    | 109½   | Special Diet |         |     |              |                   | 45      |         | 244         | +                                |                                                                  |
| 3/2   | 109¾   | Special Diet |         |     |              |                   | 45      |         | 254         | +                                |                                                                  |
| 16    | 111½   | Special Diet |         |     |              |                   | 60      |         | 273         | +                                |                                                                  |
| 27    | 111¼   | Special Diet |         |     |              |                   | 60      |         | 206         | +                                |                                                                  |
| 4/16  | 115    | Special Diet |         |     |              |                   | 60      |         | 238         | 5.0                              |                                                                  |
| 24    | 114¾   | Special Diet |         |     |              |                   | 60      |         | 252         | 25.0                             |                                                                  |
| 5/9   | 114    | Special Diet |         |     |              |                   | 60      |         | 224         | 68.0                             |                                                                  |

further decline in the urinary sugar was noted even though the vitamin intake was doubled after 14 days. The blood sugar declined very little. During the 11 days of observation the weight was constant. During the 28 days of vitamin administration there was a loss of 6½ pounds. After the vitamin was stopped, there was an immediate rise in the urine sugar to its former level, as well as in the blood sugar.

This patient has been followed in the O.P.D. for 6 weeks after discharge from the hospital. At her last observation the weight and urinary sugar and blood sugar were approximately at the same levels as upon admission.

Case No. VI: D. S., hospital No. 49281, white female, age 18, a known diabetic for ten years. Admitted to the hospital August 9, 1934, without any symptoms other than slight weakness. She had been receiving seventy-five units of insulin daily for several years. There was no history of diabetes in the family.

*Physical examination* revealed an obese patient with no abnormalities other than those resulting from her marked obesity.

*Laboratory findings:* Wassermann negative; hemoglobin 80%, r. b. c. 5,700,000, w. b. c. 16,900, poly. 68%, lymph. 30%, bas. 1%, metamyelocyte 1%; cholesterol 240 mgm.

*Analysis*—This patient was easily stabilized on her usual diet and usual intake of 75 units of insulin. On the 5th day, 20 mgms. of vitamin were administered. For the first 3 days a series of moderate hypoglycemic reactions occurred and the patient insisted upon reducing her insulin intake, even though there was only a slight decrease in the urine and blood sugar levels. On increasing the vitamin to 40 mgms. additional severe reactions occurred, and the patient rapidly reduced her insulin to 25 units, 1/3 of her previous level. Further increase of the vitamin intake to 90 mgms. daily was not attended with additional hypoglycemic reactions. The blood sugar level remained fairly constant during the study, but the urinary sugar output was 4-5 times larger than that before the vitamin was administered and the insulin was reduced. During the period of vitamin administration she lost 11 pounds in weight.

On discharge from the hospital on 9/15/35, she was maintaining her same diet with only 25 units of insulin. Follow up studies continued while this patient was away at college. Reports showed an increasing demand for insulin up to 60 units. During this time the weight increased to the level on admission to the hospital. The blood sugar levels were markedly downwards and the urine sugar was reported negative.

On April 5, while at college, a second course of vitamin therapy was instituted. 10 mgms. daily were given. A very similar series of events occurred during the second administration, as were noted during the first, namely: hypoglycemic reaction, a reduction of the insulin intake from 60 to 42 units, a doubling of the blood sugar, and a urinary sugar output of 91½ gms. (last report) although during all this time the diet remained identical.

Case No. VII: M. W., hospital No. 50199, white male, age 55, a known diabetic for three years. He has been receiving from 20 to 30 units of insulin daily for three years. Admitted to the hospital October 20, 1934, complaining of weakness, pains in the feet, coldness and loss of sensation in the feet, and attacks of fever, chills, pain and swelling of the right foot. There was no history of diabetes in the family.

*Physical examination* revealed a thin, pale, undernourished patient. Positive findings showed poor heart sounds, accentuated second aortic, liver enlarged one finger breadth below c.m., bilateral ptosis of the lids, absent k.j.'s and a.j.'s, equivocal left Babinski, suggestive Romberg, diminished sensation over both feet and legs up to the knees. Oseillometric readings show slightly diminished pulsations in both lower legs.

*Laboratory findings:* Blood and spinal Wassermann's negative, hb. 78%, r. b. c. 4,640,000, w. b. c. 7,600, differential normal; urea n. 21.6 m.g.m., creatinine 1.7 mgm., uric acid 3.4 mg. E.C.G. showed slurred Q.R.S., notched P, and left axis deviation.

*Analysis*—This patient was stabilized fairly readily. On the 7th day, 6 mgms. of vitamin were given and one week later was increased to 10 mgms. for 6 days, and then increased to 20 mgms. for 18 days more. Following the administration of the vitamin, there was a marked, although irregular increase in the urinary sugar output, which seemed to bear some relationship in time, to the increase in the amount of vitamin given. The blood sugar level increased somewhat, but not in proportion to the urinary sugar level. During the period of vitamin administration, he lost 5 pounds in weight. Upon discharge from the hospital, the blood sugar level increased, and he was finally placed upon insulin. He is still under observation in the O.P.D. and at last observation 5 months after discharge he was taking 60 units of insulin and had gained 8 pounds.

Although the studies reported in this communication are confined entirely to observations relating to the carbohydrate metabolism, the clinical picture of this patient underwent such a marked change immediately after receiving the vitamin, that it is worthy of recording. There was complete disappearance of the pain and paresthesia in both lower extremities, and the patient was able to walk easily without the use of a cane. This improvement was noted within the first week of the vitamin administration. It continued for two months after discharge. In the last 3 months there is a slight recurrence of pain.

Case No. VIII: P. D., hospital No. 50335, white female, age 6, a known diabetic for 2½ years. She has been receiving 40 units of insulin daily. Admitted to the hospital October 29, 1934, with no complaints. One maternal uncle has diabetes.

*Physical examination* revealed a well nourished young child who seems to be in good health. No abnormal findings were noted.

*Laboratory findings:* Wassermann and Kahn negative. Hg. 78%, r. b. c. 4,800,000; w. b. c. 9,800; differential normal, sedimentation time 4 mm. in 45 min., urea N. 15 mgm., creatinine 1.4; E.C.G. normal except for sinus arrhythmia.

*Analysis*—This patient could not be brought to a state of stabilization. After 12 days of preliminary observation, the vitamin was begun, at first in 2 mgm. doses (because of her age) and then in increasing doses up to 24 mgm. The period of vitamin intake covered 27 days. There was an increase in both urinary and blood sugars while taking the vitamin, but the increase was irregular. There was some suggestion of a relationship between vitamin increase and increase in urinary and blood sugar. Shortly after the vitamin was begun a questionable hypoglycemic reaction occurred with a low blood sugar. The insulin was reduced 5 units daily for 9 days and then increased 3 units for 11 days. There was little change in the levels

associated with the insulin variation. The patient lost 2 pounds during the experimental period.

No follow up studies have been possible in this patient, but reports by mail state that her condition is the same as when first seen.

Case No. IX: B. R., hospital No. 51244, white female, age 58, a known diabetic for over four years. She has been receiving insulin for the four years, taking 40 units daily. Admitted to the hospital January 11, 1935, com-

plaining of polyuria, polydipsia, genital pruritis and generalized joint pains. One aunt has diabetes.

Physical examination revealed a slightly obese patient. No pertinent abnormal findings were noted.

Laboratory findings: Wassermann and Kahn negative. Hb. 85%, r. b. c. 5,240,000, w. b. c. 8,700, differential normal, urea N. 11.2, creatinine 1.4 mgm. cholesterol 300 mgm.; B.M.R. plus 21, E.C.G. showed inverted T 3, and left axis deviation.

Analysis—This patient was fairly well stabilized after 13 days of hospitalization. Following the administration of the vitamin, in 10 mgm. doses, there was little, if any change in either urine or blood sugar levels. Patient lost 7 pounds during the period of

vitamin feeding. When the vitamin was stopped the urine and blood sugar levels remained unaltered, and since discharge for a period of 2 months follow up has shown very little change. There has been a gain of at least 6 pounds since discharge.

Case No. X: D. H., hospital No. 51241, white female, age 48, a known diabetic for over eight years. She has been taking 30 units of insulin per day for the past seven years. Admitted to the hospital on January 11, 1935, com-

| DATE  | WEIGHT | CALORIES | PROTEIN | FAT | CARBOHYDRATE | AVAILABLE GLUCOSE | INSULIN | VITAMIN | BLOOD SUGAR | GMS. URINE SUGAR PER 24 HOURS | CASE NO. 8—P. D.<br>Hospital No. 50335<br><br>REMARKS |
|-------|--------|----------|---------|-----|--------------|-------------------|---------|---------|-------------|-------------------------------|-------------------------------------------------------|
| 1934  |        |          |         |     |              |                   |         |         |             |                               |                                                       |
| 10/29 | 51½    | 1020     | 60      | 100 | 220          | 258               | 11      |         |             | 16.2                          |                                                       |
| 30    | 52     | "        | "       | "   | "            | "                 | 33      |         |             | 30.5                          |                                                       |
| 31    | 52     | "        | "       | "   | "            | "                 | 33      |         | 132         | 61.2                          |                                                       |
| 11/1  | 51½    | "        | "       | "   | "            | "                 | 33      |         |             |                               |                                                       |
| 2     | 52     | "        | "       | "   | "            | "                 | 33      |         | 55          | 20                            |                                                       |
| 3     | 52½    | "        | "       | "   | "            | "                 | 33      |         |             | 35                            |                                                       |
| 4     | 51     | "        | "       | "   | "            | "                 | 33      |         |             | 12.5                          |                                                       |
| 5     | 51½    | "        | "       | "   | "            | "                 | 33      |         |             | 36                            |                                                       |
| 6     | 51¾    | "        | "       | "   | "            | "                 | 33      |         |             | 91.3                          |                                                       |
| 7     | 52     | "        | "       | "   | "            | "                 | 33      |         | 144         | 59.8                          | Faint trace acetone                                   |
| 8     | 52     | "        | "       | "   | "            | "                 | 33      |         |             | 47.5                          |                                                       |
| 9     | 51¾    | "        | "       | "   | "            | "                 | 33      |         | 178         | 45                            |                                                       |
| 10    | 52     | "        | "       | "   | "            | "                 | 33      | 2       |             | 35.6                          |                                                       |
| 11    | 52½    | "        | "       | "   | "            | "                 | 33      | 2       |             | 28                            |                                                       |
| 12    | 51¾    | "        | "       | "   | "            | "                 | 33      | 2       | 168         | 84                            |                                                       |
| 13    | 51½    | "        | "       | "   | "            | "                 | 33      | 4       |             | 82.8                          |                                                       |
| 14    | 52     | "        | "       | "   | "            | "                 | 28      | 4       | 66          | 47.2                          | Insulin reduced 5 units                               |
| 15    | 51¾    | "        | "       | "   | "            | "                 | 28      | 4       |             | 126.5                         |                                                       |
| 16    | 51½    | "        | "       | "   | "            | "                 | 28      | 4       | 182         | 110                           |                                                       |
| 17    | 52     | "        | "       | "   | "            | "                 | 28      | 4       |             | 175                           |                                                       |
| 18    | 51     | "        | "       | "   | "            | "                 | 28      | 4       |             | 102.5                         |                                                       |
| 19    | 52     | "        | "       | "   | "            | "                 | 28      | 4       | 172         | 140                           | Faint trace of acetone                                |
| 20    | 51½    | "        | "       | "   | "            | "                 | 28      | 6       |             | 137                           |                                                       |
| 21    | 51½    | "        | "       | "   | "            | "                 | 28      | 6       | 210         | 118                           | Trace acetone                                         |
| 22    | 50¾    | "        | "       | "   | "            | "                 | 28      | 6       |             | 188                           | Faint trace acetone                                   |
| 23    | 51     | "        | "       | "   | "            | "                 | 28      | 8       | 236         | 110                           | Faint trace acetone                                   |
| 24    | 51     | "        | "       | "   | "            | "                 | 28      | 10      |             | 125                           | Two plus acetone                                      |
| 25    | 51½    | "        | "       | "   | "            | "                 | 28      | 10      |             | 115                           | Vomiting, two plus acetone                            |
| 26    | 50½    | "        | "       | "   | "            | "                 | 31      | 10      | 242         | 80                            | Insulin increased                                     |
| 27    | 51     | 1795     | "       | 75  | "            | 255               | 31      | 10      |             | 110                           | Faint trace acetone                                   |
| 28    | 51     | "        | "       | "   | "            | "                 | 31      | 10      | 262         | 76                            | Faint trace acetone                                   |
| 29    | 49     | "        | "       | "   | "            | "                 | 31      | 10      |             | 89.6                          | Concentrated vit. B 1                                 |
| 30    | 49½    | "        | "       | "   | "            | "                 | 31      | 10      | 214         | 61.6                          |                                                       |
| 12/1  | 50¾    | "        | "       | "   | "            | "                 | 31      | 14      |             | 66.5                          |                                                       |
| 2     | 50½    | "        | "       | "   | "            | "                 | 31      | 14      |             | 66.5                          |                                                       |
| 3     | 51     | "        | "       | "   | "            | "                 | 31      | 14      | 218         | 100                           |                                                       |
| 4     | 50½    | "        | "       | "   | "            | "                 | 31      | 20      |             | 85.7                          |                                                       |
| 5     | 50     | "        | "       | "   | "            | "                 | 31      | 20      | 240         | 65.4                          |                                                       |
| 6     | 50     | "        | "       | "   | "            | "                 | 31      | 24      |             | 95.2                          |                                                       |
| 7     | 50     | "        | "       | "   | "            | "                 | 31      | 24      | 236         | 95                            | Patient discharged                                    |

plaining of polyuria, polydipsia, genital pruritis and generalized joint pains. One aunt has diabetes.

Physical examination revealed a slightly obese patient. No pertinent abnormal findings were noted.

Laboratory findings: Wassermann and Kahn negative. Hb. 85%, r. b. c. 5,240,000, w. b. c. 8,700, differential normal, urea N. 11.2, creatinine 1.4 mgm. cholesterol 300 mgm.; B.M.R. plus 21, E.C.G. showed inverted T 3, and left axis deviation.

Analysis—This patient was fairly well stabilized after 13 days of hospitalization. Following the administration of the vitamin, in 10 mgm. doses, there was little, if any change in either urine or blood sugar levels. Patient lost 7 pounds during the period of

plaining of slight weakness, and occasional nocturia. One brother and one sister have diabetes.

Physical examination revealed a well nourished patient. Positive findings showed poor heart sounds, pulse rate 58, blood pressure 92/56.

Laboratory findings: Wassermann and Kahn negative; hb. 75%, r. b. c. 4,640,000, w. b. c. 8,600, normal differential; sedimentation time normal; urea nit. 12.9 mgm., creatinine 1.5 mgm., cholesterol 242 mgm., B.M.R. minus 15, E.C.G. showed inverted and notched P<sub>2</sub>, inverted T<sub>2</sub> and left axis deviation.

Analysis—This patient was extremely difficult to stabilize. After 27 days of preliminary hospitalization the insulin was stopped and the vitamin begun. Very

little change was noted during the period of experimental study. The blood and urinary sugar levels increased. This increase occurred simultaneously with the withdrawal of the insulin, and appears to be in proportion to the amount of insulin withheld. After 28 days of vitamin administration, the vitamin was stopped. The patient was observed in the hospital for 9 days more and in the O. P. D. for almost 2 months.

for the past 4 years. Admitted to the hospital February 5, 1935, complaining of genital pruritis, precordial pain radiating to the left arm, dyspnoea, ankle oedema at night, polyuria, cramps in both legs at night. There is no history of diabetes in the family.

Physical examination revealed a slightly obese patient. Positive findings showed cardiac enlargement to the left, accentuated A<sub>2</sub>, blood pressure 156/90, thickened peripheral arteries.

| DATE | WEIGHT | CALORIES | PROTEIN      | FAT | CARBOHYDRATE | AVAILABLE GLUCOSE | INSULIN | VITAMIN | BLOOD SUGAR | GMS. URINE SUGAR PER 24 HOURS | CASE NO. 9—B. R.<br>Hospital No. 51244<br><br>REMARKS |
|------|--------|----------|--------------|-----|--------------|-------------------|---------|---------|-------------|-------------------------------|-------------------------------------------------------|
| 1935 |        |          |              |     |              |                   |         |         |             |                               |                                                       |
| 1/11 | 155½   | 1615     | 60           | 75  | 175          | 210               |         |         |             | 71.0                          |                                                       |
| 12   | 155    | "        | "            | "   | "            | "                 |         |         | 294         | 100.5                         |                                                       |
| 13   | 152½   | "        | "            | "   | "            | "                 |         |         |             | 103.7                         |                                                       |
| 14   | 151½   | "        | "            | "   | "            | "                 |         |         | 297         | 111.2                         |                                                       |
| 15   | 152    | "        | "            | "   | "            | "                 |         |         |             | 128.0                         |                                                       |
| 16   | 153½   | "        | "            | "   | "            | "                 |         |         | 303         | 83.7                          |                                                       |
| 17   | "      | "        | "            | "   | "            | "                 |         |         |             | 66.0                          |                                                       |
| 18   | 151½   | "        | "            | "   | "            | "                 |         |         | 300         | 65.0                          |                                                       |
| 19   | 152½   | "        | "            | "   | "            | "                 |         |         |             | 89.2                          |                                                       |
| 20   | 151    | "        | "            | "   | "            | "                 |         |         |             | 65.0                          |                                                       |
| 21   | 151½   | "        | "            | "   | "            | "                 |         |         | 294         | 51.2                          |                                                       |
| 22   | 151½   | "        | "            | "   | "            | "                 |         |         |             | 65.1                          |                                                       |
| 23   | 150½   | "        | "            | "   | "            | "                 |         |         | 280         | 68.0                          |                                                       |
| 24   | 150    | "        | "            | "   | "            | "                 |         | 10      |             | 60.0                          |                                                       |
| 25   | 149¼   | "        | "            | "   | "            | "                 |         | 10      | 280         | 88.7                          |                                                       |
| 26   | 149¼   | "        | "            | "   | "            | "                 |         | 10      |             | 85.0                          |                                                       |
| 27   | 149¼   | "        | "            | "   | "            | "                 |         | 10      |             | 41.5                          |                                                       |
| 28   | 148½   | "        | "            | "   | "            | "                 |         | 10      | 266         | 69.3                          |                                                       |
| 29   | 148½   | "        | "            | "   | "            | "                 |         | 10      |             | 109.5                         |                                                       |
| 30   | 149½   | "        | "            | "   | "            | "                 |         | 10      | 236         | 90.0                          |                                                       |
| 31   | 149¼   | "        | "            | "   | "            | "                 |         | 10      |             | 130.0                         |                                                       |
| 2/1  | 148    | "        | "            | "   | "            | "                 |         | 10      | 290         | 105.0                         |                                                       |
| 2    | 148¼   | "        | "            | "   | "            | "                 |         | 10      |             | 100.0                         |                                                       |
| 3    | 148¼   | "        | "            | "   | "            | "                 |         | 10      |             | 104.0                         |                                                       |
| 4    | 147¼   | "        | "            | "   | "            | "                 |         | 10      | 294         | 102.0                         |                                                       |
| 5    | 148¼   | "        | "            | "   | "            | "                 |         | 10      |             | 100.0                         |                                                       |
| 6    | 148½   | "        | "            | "   | "            | "                 |         | 10      | 276         | 99.0                          |                                                       |
| 7    | 148¼   | "        | "            | "   | "            | "                 |         | 10      |             | 92.0                          |                                                       |
| 8    | 147    | "        | "            | "   | "            | "                 |         | 10      | 282         | 90.0                          |                                                       |
| 9    | 148    | "        | "            | "   | "            | "                 |         | 10      |             | 66.0                          |                                                       |
| 10   | 148    | "        | "            | "   | "            | "                 |         | 10      |             | 80.0                          |                                                       |
| 11   | 147    | "        | "            | "   | "            | "                 |         | 10      | 292         | 110.0                         |                                                       |
| 12   | 149    | "        | "            | "   | "            | "                 |         | 10      |             | 100.0                         |                                                       |
| 13   | 146½   | "        | "            | "   | "            | "                 |         | 10      | 282         | 132.0                         |                                                       |
| 14   | 146    | "        | "            | "   | "            | "                 |         | 10      |             | 70.0                          |                                                       |
| 15   | 147¼   | "        | "            | "   | "            | "                 |         | 10      | 266         | 108.0                         |                                                       |
| 16   | 146    | "        | "            | "   | "            | "                 |         | 10      |             | 66.0                          |                                                       |
| 17   | 146¼   | "        | "            | "   | "            | "                 |         | 10      |             | 72.6                          |                                                       |
| 18   | 145½   | "        | "            | "   | "            | "                 |         | 10      | 276         | 84.0                          |                                                       |
| 19   | 146½   | "        | "            | "   | "            | "                 |         | 10      |             | 68.0                          |                                                       |
| 20   | 146    | "        | "            | "   | "            | "                 |         | 10      | 268         | 42.0                          |                                                       |
| 21   | 145    | "        | "            | "   | "            | "                 |         |         |             | 70.0                          |                                                       |
| 22   | 143    | "        | "            | "   | "            | "                 |         |         |             | 80.0                          |                                                       |
| 23   | 143¼   | "        | "            | "   | "            | "                 |         |         | 278         |                               | Patient discharged                                    |
| 3/6  | 149½   |          | Special Diet |     |              |                   |         |         | 327         | +                             | Follow-up O.P.D.                                      |
| 27   | 149    |          | Special Diet |     |              |                   | 30      |         | 366         | +                             | All weights with clothes                              |
| 4/11 | 151½   |          | Special Diet |     |              |                   | 20      |         | 336         | 12.0                          |                                                       |
| 5/1  | 155½   |          | Special Diet |     |              |                   | 30      |         | 339         | 150.0                         |                                                       |

Her blood and urinary sugar levels are about the same as they were when the insulin was stopped. During the time of vitamin administration, the patient lost about 4 pounds in weight. None of this has been regained.

Case No. XI: S. B., hospital No. 51559, white female, age 48, a known diabetic for nine years. She has been taking insulin for over seven years, using 40 units daily

Laboratory findings: Wassermann and Kahn negative; hb. 85%, r. b. c. 5,120,000; w. b. c. 12,600; normal differential, sedimentation time 10 mm. in 45 min., urea N. 11.8 mgm., creatinine 1.4 mgm., cholesterol 306 mgm., B.M.R. minus 9, E.C.G. notched Q.R.S., and 1, high voltage, and left axis deviation.

Analysis—This patient was fairly readily stabilized, and after 10 days of hospitalization 10 mgms. of

| DATE | WEIGHT | CALORIES | PROTEIN      | FAT | CARBOHYDRATE | AVAILABLE GLUCOSE | INSULIN | VITAMIN | BLOOD SUGAR | GMS. URINE SUGAR<br>PER 24 HOURS | CASE NO. 10—D. H.<br>Hospital No. 51241 | REMARKS                  |
|------|--------|----------|--------------|-----|--------------|-------------------|---------|---------|-------------|----------------------------------|-----------------------------------------|--------------------------|
| 1935 |        |          |              |     |              |                   |         |         |             |                                  |                                         |                          |
| 1/11 | 147½   | 1615     | 60           | 75  | 175          | 210               | 30      |         |             | 6.9                              |                                         |                          |
| 12   | 145    | "        | "            | "   | "            | "                 | 30      |         | 188         | 5.8                              |                                         |                          |
| 13   | 143½   | "        | "            | "   | "            | "                 | 30      |         |             | 14.5                             |                                         |                          |
| 14   | 142¼   | "        | "            | "   | "            | "                 | 30      |         | 255         | 10.5                             |                                         |                          |
| 15   | 142½   | "        | "            | "   | "            | "                 | 30      |         |             | 5                                |                                         |                          |
| 16   | 143¼   | "        | "            | "   | "            | "                 | 30      |         | 238         | 8.2                              |                                         |                          |
| 17   | "      | "        | "            | "   | "            | "                 | 30      |         |             | 25                               |                                         |                          |
| 18   | 142½   | "        | "            | "   | "            | "                 | 30      |         | 236         | 5.7                              |                                         |                          |
| 19   | 142¼   | "        | "            | "   | "            | "                 | 30      |         |             | 7.7                              |                                         |                          |
| 20   | 143    | "        | "            | "   | "            | "                 | 30      |         |             | 6.5                              |                                         |                          |
| 21   | 143¾   | "        | "            | "   | "            | "                 | 30      |         | 236         | 0                                |                                         |                          |
| 22   | 143¼   | "        | "            | "   | "            | "                 | 30      |         |             | 0                                |                                         |                          |
| 23   | 143¾   | "        | "            | "   | "            | "                 | 30      |         | 230         | 5.3                              |                                         |                          |
| 24   | 144    | "        | "            | "   | "            | "                 | 30      |         |             | 0                                |                                         |                          |
| 25   | 143½   | "        | "            | "   | "            | "                 | 25      |         | 232         | 3.9                              |                                         | Insulin reduced          |
| 26   | 143¾   | "        | "            | "   | "            | "                 | 25      |         |             | 2.3                              |                                         |                          |
| 27   | 143    | "        | "            | "   | "            | "                 | 20      |         |             | 11.2                             |                                         | Insulin reduced          |
| 28   | 142¾   | "        | "            | "   | "            | "                 | 20      |         | 228         | 0                                |                                         |                          |
| 29   | 143¼   | "        | "            | "   | "            | "                 | 20      |         |             | 5.2                              |                                         |                          |
| 30   | 142    | "        | "            | "   | "            | "                 | 20      |         | 334         | 7.2                              |                                         | Emotional upset          |
| 31   | 142½   | "        | "            | "   | "            | "                 | 20      |         |             | 0                                |                                         |                          |
| 2/1  | 142½   | "        | "            | "   | "            | "                 | 10      |         | 232         | 13                               |                                         | Insulin reduced          |
| 2    | 142½   | "        | "            | "   | "            | "                 | 10      |         |             | 11.4                             |                                         |                          |
| 3    | 142    | "        | "            | "   | "            | "                 | 10      |         |             | 26                               |                                         |                          |
| 4    | 141½   | "        | "            | "   | "            | "                 | 10      |         | 248         | 19                               |                                         |                          |
| 5    | 141¼   | "        | "            | "   | "            | "                 | 0       |         |             | 46                               |                                         | Insulin stopped          |
| 6    | 141½   | "        | "            | "   | "            | "                 |         |         | 300         | 43.5                             |                                         |                          |
| 7    | 141¾   | "        | "            | "   | "            | "                 |         |         |             | 71                               |                                         |                          |
| 8    | 141¾   | "        | "            | "   | "            | "                 |         | 10      | 294         | 49.3                             |                                         |                          |
| 9    | 141    | "        | "            | "   | "            | "                 |         | 10      |             | 53.2                             |                                         |                          |
| 10   | 141¼   | "        | "            | "   | "            | "                 |         | 10      |             | 89                               |                                         |                          |
| 11   | 140    | "        | "            | "   | "            | "                 |         | 10      | 327         | 52.5                             |                                         |                          |
| 12   | 140    | "        | "            | "   | "            | "                 |         | 10      |             | 92.2                             |                                         |                          |
| 13   | 139¼   | "        | "            | "   | "            | "                 |         | 10      | 333         | 114                              |                                         |                          |
| 14   | 139¼   | "        | "            | "   | "            | "                 |         | 10      |             | 60.3                             |                                         |                          |
| 15   | 139¼   | "        | "            | "   | "            | "                 |         | 10      | 318         | 100                              |                                         |                          |
| 16   | 140¾   | "        | "            | "   | "            | "                 |         | 10      |             | 100                              |                                         |                          |
| 17   | 141¼   | "        | "            | "   | "            | "                 |         | 10      |             | 120                              |                                         |                          |
| 18   | 140¼   | "        | "            | "   | "            | "                 |         | 10      | 336         | 68                               |                                         |                          |
| 19   | 140¾   | "        | "            | "   | "            | "                 |         | 10      |             | 100                              |                                         |                          |
| 20   | 140    | "        | "            | "   | "            | "                 |         | 10      | 327         | 100                              |                                         | Concentrated vit. B 1    |
| 21   | 139¼   | "        | "            | "   | "            | "                 |         | 10      |             | 66                               |                                         |                          |
| 22   | 140    | "        | "            | "   | "            | "                 |         | 10      |             | 75                               |                                         |                          |
| 23   | 139½   | "        | "            | "   | "            | "                 |         | 10      | 333         | 105                              |                                         |                          |
| 24   | 139½   | "        | "            | "   | "            | "                 |         | 10      |             | 28.6                             |                                         |                          |
| 2/25 | 139¼   | "        | "            | "   | "            | "                 |         | 10      | 321         | 62                               |                                         |                          |
| 26   | 139½   | "        | "            | "   | "            | "                 |         | 10      |             | 120                              |                                         |                          |
| 27   | 139¼   | "        | "            | "   | "            | "                 |         | 10      | 306         | 96                               |                                         |                          |
| 28   | 138½   | "        | "            | "   | "            | "                 |         | 10      |             | 96                               |                                         |                          |
| 3/1  | 137½   | "        | "            | "   | "            | "                 |         | 10      | 312         | 100                              |                                         |                          |
| 2    | 137    | "        | "            | "   | "            | "                 |         | 10      |             |                                  |                                         | Urine not examined       |
| 3    | 136¾   | "        | "            | "   | "            | "                 |         | 10      |             | 88                               |                                         |                          |
| 4    | 137¼   | "        | "            | "   | "            | "                 |         | 10      | 324         | 117.5                            |                                         |                          |
| 5    | 137    | "        | "            | "   | "            | "                 |         | 20      |             | 92                               |                                         | Vitamin increased        |
| 6    | 137¼   | "        | "            | "   | "            | "                 |         | 20      | 333         | 110                              |                                         |                          |
| 7    | 138    | "        | "            | "   | "            | "                 |         | 20      |             | 69.3                             |                                         |                          |
| 8    | 137¼   | "        | "            | "   | "            | "                 |         |         | 309         | 47.5                             |                                         | Vit. min stopped         |
| 9    | 137¾   | "        | "            | "   | "            | "                 |         |         |             | 110                              |                                         |                          |
| 10   | 136½   | "        | "            | "   | "            | "                 |         |         |             | 115                              |                                         |                          |
| 11   | 135¾   | "        | "            | "   | "            | "                 |         |         | 254         | 100                              |                                         |                          |
| 12   | 136¾   | "        | "            | "   | "            | "                 |         |         |             | 70                               |                                         |                          |
| 13   | 137    | "        | "            | "   | "            | "                 |         |         | 336         | 80                               |                                         |                          |
| 14   | 137    | "        | "            | "   | "            | "                 |         |         |             | 112                              |                                         |                          |
| 15   | 137½   | "        | "            | "   | "            | "                 |         |         | 312         | 115                              |                                         |                          |
| 16   | 137    | "        | "            | "   | "            | "                 |         |         |             |                                  |                                         | Patient discharged       |
| 3/21 | 140    |          | Special Diet |     |              |                   | 0       |         | 303         | +                                |                                         | Follow-up in O.P.D.      |
| 4/4  | 138½   |          | Special Diet |     |              |                   | 0       |         | 312         | 64                               |                                         | All weights with clothes |
| 5/4  | 137    |          | Special Diet |     |              |                   | 0       |         | 312         | 120                              |                                         |                          |

vitamin B<sub>1</sub> was begun. For 28 days 10 mgms. first, and later 20 mgms. were administered daily. During this period of time no change in the blood or urine sugar levels was noted. The patient lost 6 pounds in weight during the time of the vitamin administration. She has been observed for about 6 weeks since dis-

worse at the time administration of the vitamin was begun. This was particularly true of those whose intake of insulin had been reduced.

The brevity of the interval between the administration of the vitamin and the lowering of the blood sugar and urinary sugar also argues for a causal relation-

| DATE | WEIGHT  | CALORIES | PROTEIN      | FAT | CARBOHYDRATE | AVAILABLE GLUCOSE | INSULIN | VITAMIN | BLOOD SUGAR | GMS. URINE SUGAR PER 24 HOURS | CASE NO. 11—S. B.<br>Hospital No. 51559<br><br>REMARKS |
|------|---------|----------|--------------|-----|--------------|-------------------|---------|---------|-------------|-------------------------------|--------------------------------------------------------|
| 1935 |         |          |              |     |              |                   |         |         |             |                               |                                                        |
| 2 5  |         | 1515     | 60           | 75  | 175          | 210               |         |         |             | 17.5                          | Urine less than 24 hr. spec.                           |
| 6    | 176 1/4 | 1775     | 75           | 75  | 200          | 242               |         |         | 282         | 124.7                         |                                                        |
| 7    | 176 1/2 | "        | "            | "   | "            | "                 |         |         |             | 112                           |                                                        |
| 8    | 176 1/2 | "        | "            | "   | "            | "                 |         |         | 272         | 82.5                          |                                                        |
| 9    | 177     | "        | "            | "   | "            | "                 |         |         |             | 75                            |                                                        |
| 10   | 177     | "        | "            | "   | "            | "                 |         |         |             | 90                            |                                                        |
| 11   | 175 1/4 | "        | "            | "   | "            | "                 |         |         | 288         | 70                            |                                                        |
| 12   | 175     | "        | "            | "   | "            | "                 |         |         |             | 72.5                          |                                                        |
| 13   | 174     | "        | "            | "   | "            | "                 |         |         | 231         | 105                           |                                                        |
| 14   | 174 1/2 | "        | "            | "   | "            | "                 |         |         |             | 91.7                          |                                                        |
| 15   | 174 1/2 | "        | "            | "   | "            | "                 |         |         | 242         | 65                            |                                                        |
| 16   | 174 1/4 | "        | "            | "   | "            | "                 |         | 10      |             | 65                            |                                                        |
| 17   | 174 1/4 | "        | "            | "   | "            | "                 |         | 10      |             | 56                            |                                                        |
| 18   | 174 1/4 | "        | "            | "   | "            | "                 |         | 10      | 260         | 72.5                          |                                                        |
| 19   | 173 1/4 | "        | "            | "   | "            | "                 |         | 10      |             | 52                            |                                                        |
| 20   | 173 1/4 | "        | "            | "   | "            | "                 |         | 10      | 244         | 91                            |                                                        |
| 21   | 173     | "        | "            | "   | "            | "                 |         | 10      |             | 70                            | Concentrated vit. B 1                                  |
| 22   | 172 1/2 | "        | "            | "   | "            | "                 |         | 10      |             | 60                            |                                                        |
| 23   | 173     | "        | "            | "   | "            | "                 |         | 10      | 264         | 78                            |                                                        |
| 24   | 172 1/2 | "        | "            | "   | "            | "                 |         | 10      |             | 21                            |                                                        |
| 25   | 172 1/2 | "        | "            | "   | "            | "                 |         | 10      | 242         | 72                            |                                                        |
| 26   | 172 1/2 | "        | "            | "   | "            | "                 |         | 10      |             | 78                            |                                                        |
| 27   | 172     | "        | "            | "   | "            | "                 |         | 10      | 238         | 75                            |                                                        |
| 28   | 171     | "        | "            | "   | "            | "                 |         | 10      |             | 90                            |                                                        |
| 3 1  | 170     | "        | "            | "   | "            | "                 |         | 10      | 284         | 70                            |                                                        |
| 2    | 171 1/2 | "        | "            | "   | "            | "                 |         | 10      |             |                               | Urine not examineded                                   |
| 3    | 171     | "        | "            | "   | "            | "                 |         | 10      |             | 39.6                          |                                                        |
| 4    | 171 1/2 | "        | "            | "   | "            | "                 |         | 10      | 262         | 37.9                          |                                                        |
| 5    | 171 1/4 | "        | "            | "   | "            | "                 |         | 20      |             | 28                            | Vit. increased                                         |
| 6    | 171 1/2 | "        | "            | "   | "            | "                 |         | 20      | 254         | 47.5                          |                                                        |
| 7    | 170 1/2 | "        | "            | "   | "            | "                 |         | 20      |             | 75                            |                                                        |
| 8    | 169 1/2 | "        | "            | "   | "            | "                 |         | 20      | 268         | 32.5                          |                                                        |
| 9    | 170     | "        | "            | "   | "            | "                 |         | 20      |             | 42.5                          |                                                        |
| 10   | 169     | "        | "            | "   | "            | "                 |         | 20      |             | 65                            |                                                        |
| 11   | 169 1/2 | "        | "            | "   | "            | "                 |         | 20      | 290         | 60                            |                                                        |
| 12   | 168 1/2 | "        | "            | "   | "            | "                 |         | 20      |             | 64                            |                                                        |
| 13   | 168     | "        | "            | "   | "            | "                 |         | 20      | 255         | 70                            |                                                        |
| 14   | 168 1/4 | "        | "            | "   | "            | "                 |         | 20      |             | 60                            |                                                        |
| 15   | 167 1/4 | "        | "            | "   | "            | "                 |         | 20      | 288         | 70                            |                                                        |
| 16   | 168     | "        | "            | "   | "            | "                 |         | 0       |             | 60                            | Vitamin stopped                                        |
| 17   | 168 1/4 | "        | "            | "   | "            | "                 |         |         |             | 70                            |                                                        |
| 18   | 166 1/4 | "        | "            | "   | "            | "                 |         |         | 298         |                               | Patient discharged                                     |
| 3 21 |         |          | Special Diet |     |              |                   |         |         | 214         | +                             | Follow-up at home                                      |
| 4 3  |         |          | Special Diet |     |              |                   |         |         | 300         | +                             | All weights with clothes                               |
| 4 17 |         |          | Special Diet |     |              |                   |         |         | 300         | 30                            |                                                        |
| 4 30 |         |          | Special Diet |     |              |                   | 10      |         | 288         | 20                            |                                                        |

charge from the hospital with practically no change in the urine or blood sugar level.

#### RECAPITULATION

Analyzing these cases, the conclusion is inescapable that there is a direct causal relationship between the intake of the vitamin and the subsequent drop in the blood sugar and glycosuria. The elements of coincidence and dietary control may be rejected since all of the cases were fairly well stabilized. As a matter of fact, several of the patients were definitely growing

ship. Usually, the drop took place within two or three days, never after more than seven. If this effect did not manifest itself in a very short time, it did not occur throughout the entire period of the experiment.

Complementing this observation is the rapidity with which the aberration returned in two of the cases, *i. e.*, the blood sugar and glycosuria increased, when the administration of B<sub>1</sub> was discontinued. All of this points to a causal rather than coincidental relationship be-



tween the ingestion of the vitamin and the increased utilization of carbohydrates.

Additional substantiation of this theory is furnished by some of the negative cases in which administration of the vitamin not only failed to increase the utilization of carbohydrates but was followed by an aggravation of the diabetic state. This result, although adverse, confirms the influence of vitamin B<sub>1</sub> on the carbohydrate tolerance.

Once we concede the causative relationship, the question arises as to the *nature of the interaction*. Previous experiments in animals indicate that B<sub>1</sub> acts as a catalyst. This hypothesis provides a plausible explanation of the rapidity of the reaction to the vitamin. It also accounts for the fact that once an effect appears, it is not heightened by augmenting the dosage. In other words, the reaction is at its maximum as soon as it is established, and an increase in the amount of the vitamin does not produce additional consequences. In one case, the quantity necessary to bring about a positive result was multiplied nine times without intensifying the effects. This is convincing evidence that we are dealing with a catalyst rather than with a substance like insulin whose influence is proportional to the amount used.

It is interesting to speculate on the character of the reaction in those negative cases which seemed worse after ingestion of the vitamin. Bearing in mind experiments in animals in which glycogen in the liver and muscles was broken up by the addition of B<sub>1</sub>, the possibility is suggested of some irreversible chemical reaction which arrests the catalytic function of the vitamin but permits it to flood the blood stream with available carbohydrate. This theory, admittedly mere conjecture, might account for the increase in blood sugar and urinary sugar in some of the negative cases when the vitamin intake was increased.

In the course of our investigation, a careful search of the literature was made to determine whether or not other work in this field had been described. In 1928, Mills (17) reported a study of seven diabetics to whom he had administered a crude acid alcohol extract of a variety of plants, which he believed to be rich in vitamin B<sub>1</sub>. All of his cases experienced a diminution in urinary sugar. In 1933, Labbe, *et al.* (18) published the results of administration of a vegetable powder, said to possess a high vitamin B<sub>1</sub> content, to twelve cases of diabetes. Nine of these showed beneficial results. Unfortunately, neither of these reports contains detailed observations and there is no indication of adequate controls.

Minot (19), in 1929, observed two cases of diabetes associated with peripheral neuritis and achylia gastrica whose symptoms improved slightly upon taking large amounts of a yeast concentrate. Wohl (20) also reports a case of diabetes, with symptoms of beriberi, whose diabetic and neuritic manifestations improved on insulin and yeast.

In previous studies of the effect of crude extracts, containing unknown quantities of vitamin B<sub>1</sub>, upon the clinical course of diabetes mellitus, although the number of cases investigated was small and results were questionable, benefits of varying degree were reported. Our group of eleven patients, observed over a period

of months under careful controls, showed an increased utilization of carbohydrates in 54.6% of the cases upon an average daily intake of ten mgms. of vitamin B<sub>1</sub> for four weeks.

The clinical syndrome of diabetes mellitus has many features of a nutritional disturbance whose etiology is not yet known. It has been suggested that a vitamin deficiency may be conducive to its incidence, and influence its clinical course. Proceeding on this hypothesis, there is evidence that vitamin B<sub>1</sub> may be the substance in question. In view of the results of experimental work in animals, of biochemical research, and the clinical studies reported herewith, it is urged that further investigations be conducted to determine the effects of large amounts of this vitamin in diabetes mellitus.

#### SUMMARY AND CONCLUSIONS

1. Experimental deficiency of vitamin B<sub>1</sub> causes a disturbance of the carbohydrate metabolism characterized by a rise in the blood sugar and in the glycogen content of liver and muscle. Although a diminished carbohydrate tolerance is encountered in other forms of avitaminosis and aberration from the normal state, it is most consistent and marked in experimental B<sub>1</sub> deficiency.

2. The clinical syndrome of diabetes mellitus is suggestive of a nutritional disturbance and there is reason to think that a deficiency of vitamin B<sub>1</sub> may be a factor in the production and clinical course of this condition.

3. In a series of eleven cases of proven diabetes mellitus (according to present day standards) to whom an average of ten mgms. of vitamin B<sub>1</sub> were administered daily for twenty-eight consecutive days, six (or 54.6%) showed an increased carbohydrate utilization. Five cases (45.4%) showed no increase. Two of the six positive cases lost the gain in carbohydrate utilization as soon as the administration of vitamin B<sub>1</sub> was stopped. In four cases, the increase continued for periods ranging from two to ten months. Two of these four are still maintaining the gain.

4. Further study of this problem is merited.

#### DISCUSSION:

DR. JOSEPH T. BEARDWOOD, JR. (Philadelphia, Pa.): Through the courtesy of Dr. Vorhaus, I was able to try this vitamin on three patients on my service at the Hospital of the Graduate School of the University of Pennsylvania. My experience, therefore, has been very limited and possibly the choice of cases not altogether so great as one might wish, but from these cases, the histories of which I will briefly detail, we fail to find very marked alteration in the carbohydrate metabolism which we would attribute to the action of the vitamin alone.

There were three cases in which we used the vitamin: First, a man of thirty-five, who had known that he had diabetes for about four years. He was admitted and placed on a 2100 caloric diet, consisting of 140 grams of carbohydrate, 70 grams of protein, and 140 of fat, and his blood sugar varied to 243 from 220, without insulin. He was placed on the vitamin for a period of ten days, at which time his blood sugars ran from 200 to 210, and we then placed him on insulin. He was standardized readily on 57 units a day, and on discharge he required 46 units a day.

The second was a case of a woman of fifty-three, who on a maintenance diet ran sugar between 112 and 160

without vitamin and over a period of ten days with the use of vitamin, the sugar varied between 144 and 153. She showed no urinary sugar at any time.

The third case was a case which had a blood sugar of about 145 to 150 on a normal maintenance diet. She had a B.M.R. of plus twenty and had some gall bladder disease. With the use of vitamin her blood sugar varied between 110 to 122. This was the only case which showed any marked change, that we felt could be attributed to the vitamin, although the blood sugar started to come down before vitamin was administered.

I should like to emphasize that on a maintenance diet, we normally often find a decrease in the blood sugar over a period of time. This drop sometimes may take ten days or two or three weeks before it is made manifest, but it does occur in practically all diabetics except severe ones, and we must bear this in mind in evaluating any method of treatment. The type of diet is of importance. We feel that the amount of carbohydrate in the diet, if it be high enough, has relatively little to do with the amount of insulin that is required; in other words, with the higher carbohydrate diet, it is probable that diabetics, none of whom are total diabetics, as experimental animals are, are stimulated to secrete a certain amount of insulin of their own, the most important thing is to keep the total calories relatively low.

It is interesting in Dr. Vorhaus' group of cases to notice the marked change in the urinary sugar which did not always keep pace with the blood sugar.

In analyzing his cases, they all showed relatively high blood cholesterol which, of course, is a common finding in uncontrolled diabetics, but it would be interesting to note any change in the blood cholesterol as the cases were followed, because from work of Rabinowitz, it is apparently the blood cholesterol which determines to some extent the amount of insulin required to control the diabetics.

The cases in which the vitamin was active in all these series were all rather stout and from the protocols of the cases, well nourished individuals. Those in whom the vitamin had little effect were thin and underweight, except in two cases.

The average thin dietic is a severe diabetic. One would be justified in the conclusion that possibly there are several types of conditions which produce the syndrome of diabetes mellitus.

I am probably somewhat out of order when speaking to this Association, in saying that from recent work it is apparent that many cases of diabetes are not due to pancreatic disease. Metabolists feel that the number of cases of diabetes which are due to actual demonstrable diseases of the pancreas is relatively small, and it would seem logical, therefore, that if further work by Dr. Vorhaus and others show any consistent effect of the vitamin or carbohydrate metabolism that vitamin deficiency might be one factor which would produce a syndrome of diabetes mellitus. Dr. Vorhaus has been modest in his claims and I think the work merits further investigation and further report.

DR. J. EARL THOMAS (Philadelphia, Pa.): Dr. Vorhaus' paper deals with two quite distinct problems: namely, the relation between vitamin B<sub>1</sub> and carbohydrate metab-

olism; and the possible relation between Vitamin B<sub>1</sub> and diabetes mellitus.

The relationship between the vitamin and normal carbohydrate metabolism appears to be a fairly well established fact; whether that is the primary function of the vitamin in metabolism is another question, but there doesn't seem to be any doubt that deficiency of vitamin B<sub>1</sub> results in an excess of blood sugar and an excess of liver glycogen.

Considering diabetes, although there is an increase in blood sugar, there is a deficiency of liver glycogen, whereas the opposite condition develops in vitamin B deficiency. The deficiency of liver glycogen in diabetes is well known to biochemists and physiologists, and I assume also to members of the medical profession.

There is a very close and intimate relationship between all the different metabolic processes that go on in the body, and the mere fact that the administration of a vitamin in a particular disease condition improves the condition of the patient and causes an alleviation of the symptoms, doesn't in itself establish any relationship between that vitamin and the disease in question.

Now, it seems logical to suppose that many diabetics suffer from vitamin B deficiency. Vitamin B occurs mostly in cereals. Diabetics have a restricted carbohydrate diet, and unless their diet is watched carefully to see that there is a sufficiency of the vitamin, Vitamin B is likely to be deficient. Deficiency of vitamin B would almost certainly aggravate the symptoms of diabetes. It might even cause a latent diabetes to become active. If that should occur, the administration of vitamin B would unquestionably alleviate the condition to some extent though it would not cure the disease; however, such an observation would not establish a causative relationship between vitamin B deficiency and diabetes.

The most logical conclusion that I can draw from these most interesting and valuable studies is that vitamin B deficiency is likely to be an accompaniment of diabetes, and in the treatment of diabetes such condition should be looked for and, if present, treated appropriately.

DR. MARTIN G. VORHAUS (New York City, in closing): I want to take this opportunity to thank the discussants, particularly Dr. Beardwood for his efforts in studying some of these cases. It has been interesting to speculate on the points brought up; namely, as Dr. Thomas so well put it, whether or not the relationship is coincidental in diabetes, or causative.

In a small series of cases which we have shown, no definite deductions can be made. The future may answer the question.

Dr. Beardwood's observation is in accordance with ours, that perhaps some of the milder cases of so-called diabetes according to the present-day standards may turn out not to be diabetes mellitus as we understand it, but that the diabetic manifestations may be signs of a vitamin B deficiency. That question cannot be answered at the present time.

It is significant that in a certain percentage the patients show some improvement based on chemical studies, and in addition there is an improvement in the general state, which may be either non-specific or specific.

The question of blood cholesterol is being studied, but for such a short length of time that reports have not been included in the study.

## REFERENCES

1. Funk, C.: Action of Substances Influencing the Carbohydrate Metabolism in Experimental Beriberi. *J. Physiol.*, 53:247-256, 1919.
2. Roche, J.: Recherches sur le syndrome urinaire de troubles métaboliques provoqués par la carence en facteurs B chez le Rat. *Bull. de la Soc. de Chim. Biol.*, 12:342-355, 1930.
3. Koss, S. K.: On the Carbon: Nitrogen (C/N) Ratio in the Urine of Rats Deprived of One or Both Factors of the Vitamin B Complex. *J. Nutrition*, 1:167-173, 1929.
4. Rando, L., and Simonnet, H.: Les dominées et les inconnues du problème alimentaire. *Les Presses universitaires de France*, 1927.
5. Alderhalden, E.: Weitere Beiträge zur Kenntnis von Organischen Nahrungstoffen mit Spezifischer Wirkung. (A group of articles). *Arch. f. d. ges. Physiol.*, 195, 197, 198, 1922.
6. Alderhalden, E., and Wertheimer, E.: Beziehungen des Vitamin-B-Komplexes (insbesondere des Vitamins B<sub>1</sub>) zum Kohlehydratstoffwechsel. *Arch. f. d. ges. Physiol.*, 233:395-416, 1933.
7. Kauffmann-Cosla, O.: Experiments on dysoxidative carbonuria in avitaminosis and influence of insulin and fons on it. *Biochem. Ztschr.*, 166:253-294, 1925.
8. Kauffmann-Cosla, O.; Vassileo, O., and Oerli, S.: Experimentelle Untersuchungen über die Avitaminose B und die Bedeutung des Faktors B<sub>1</sub> und B<sub>2</sub> in der Oxydation der Zelle. *Arch. f. Exper. Path. u. Pharmacol.*, 164:604-620, 1932.

9. Kauffmann-Cosla, O., and Oeriu, S.: Die Wirkung des Insulins auf experimentelle Beriberi und experimenteller Avitaminose B. *Arch. f. Exper. Path. u. Pharmacol.*, 170:458-461, 1933.
10. Braier, B.: Le rapport carbone azote dans l'avitaminose B des chiens hypophysoprives. *Compt. rend. Soc. de Biol.*, 108:507-508, Oct. 30, 1931.
11. Collazo, J. A.: Pathogenesis of dysoxidative carbonuric. *Dtsch. Med. Wschr.*, 51:1614-1615, 1925.
12. Peters, R. A., and Sinclair, H. M.: Studies in Avian Carbohydrate Metabolism: Further Studies Upon the Action of Catechol in Brain. *Biolog. J.*, 27:1910-1926, 1933.
13. Sinclair, H. M.: The Effect of Vitamin B<sub>1</sub> upon the Respiratory Quotient of Brain Tissue. *Biolog. J.*, 27:1927-1934, 1933.
14. Thompson, R. H. C.: The Action of Crystalline Vitamin B<sub>1</sub> on the Respiration of Polyneuritic Tissues *in vitro*. *Biolog. J.*, 28:909-915.
15. Peters, R. A., and Thompson, R. H. S.: Pyruvic Acid as an Intermediary Metabolite in the Brain Tissue of Avitaminous and Normal Pigeons. *Biolog. J.*, 28:916-925.
16. Peters, R. A., and Sinclair, H. M.: Vitamin B<sub>1</sub> and Tissue Oxidation. *Arch. f. exp. Zellfor.*, 15:59-60, 1934.
17. Mills, C. A.: Treatment of Diabetes with an Acid-Alcoholic Extract of Plants Rich in Vitamin B. *Am. J. Med. Sc.*, 175:376-383, 1928.
18. Labbe, M.; Nepveux, F., and Gringoire, J. D.: Les Vitamines B dans le métabolisme du glycogène: Application au traitement du diabète. *Revue de pathologie comparée et d'hygiène général.* 33:1557-1571, December, 1933.
19. Minot, G. R.: Some Fundamental Clinical Aspects of Deficiencies. *Ann. Int. Med.*, 3:216-229, 1929.
20. Wohl, M. G.: Avitaminosis in the Course of Diabetes. *J. A. M. A.*, 87:901-906, 1925.

## Gastro-Intestinal Manifestations of Hyperinsulinism \*

By

SEALE HARRIS, M.D.  
BIRMINGHAM, ALABAMA

**H**YPOGLYCEMIC symptoms are found not infrequently in patients who suffer from the various manifestations of disorders of the stomach and other abdominal viscera. This is particularly true of patients ordinarily classed as neurotics, who go from one specialist to another for relief of "nervous indigestion." Hyperinsulinism has been found associated with peptic ulcer and gall bladder disease in a number of cases; and it may be a manifestation of both acute and chronic pancreatitis, and adenomas of the pancreas, so that the patient with a proved abdominal lesion may suffer also from the bizarre manifestations of hypoglycemia. Careful history taking in gastro-intestinal patients will elicit the information that in many of them the symptoms occur most frequently before breakfast, one or two hours before meals, and during the night. Blood sugar studies during the attacks, or when fasting, and dextrose tolerance tests carried out for six hours will reveal not infrequently the hypoglycemia that is the *sine qua non* in the diagnosis of hyperinsulinism, which may be relieved or prevented by the proper dietary management.

Cambridge, (1) in one of the most valuable contributions to the literature on "chronic hypoglycemia," reported 200 cases in which blood sugar readings of below 0.070 per cent were found. Cambridge said: "Comparatively few cases of hypoglycemia are free from gastro-intestinal disorders; long-standing constipation is common, but frequent and offensive stools are not unusual, especially in children; and some patients have distension, flatulency and heart-burn." Cambridge believes that there is an etiologic relation between inflammatory lesions of the upper intestines and "chronic hypoglycemia." He said: "Since a chronic catarrh of the upper intestines is generally associated with an infection of the bile and pancreatic ducts, the consequent disturbance of the liver and pancreas may contribute to the low blood sugar in that type of case." He adds: "I find that patients with chronic hypogly-

cemia do not improve satisfactorily unless the bowel condition is successfully treated."

Cambridge's study of his 200 cases revealed that 32 children in whom "cyclic vomiting" was a manifestation of hypoglycemia, 84 per cent had "chronic catarrh of the intestinal tract." Thirteen of his adult patients complained of severe recurrent attacks of "bilious" vomiting, including 6 cases of pernicious vomiting of pregnancy. There were "recurrent headaches" in 25 cases; and in the 11 cases he classified as "neurasthenia," "all suffered from intestinal disturbance." Seven of Cambridge's hypoglycemics had "convulsive attacks, 4 of which were believed to have mild epilepsy." In the cases in which "lack of energy" was the principal complaint, "75 per cent had evidences of infection in the upper part of the abdomen." Twenty-two cases of "chronic hypoglycemia" were found in patients who had been rejected for life insurance on account of sugar in the urine; and in "75 per cent of these there were evidences of intestinal trouble."

Cambridge found 48 patients with abnormally low blood sugars during the course of routine examinations. Of these "the majority had obscure disturbances of digestion or metabolism." Six were obese; 4 had gall bladder disease; 2, pernicious anemia; 1, cancer of the pancreas; and in 1 child there was delayed development. Cambridge's analysis of his 200 cases of "chronic hypoglycemia" proves the value of routine blood sugar studies on gastro-intestinal patients.

Cambridge (2) in another article on the chronic hypoglycemia as an operative risk said: "Several chronic hypoglycemics had previously been operated upon for duodenal ulcer with unsatisfactory results. In others the removal of the appendix was followed by serious vomiting and ketoses which were relieved by intravenous injections of glucose."

There were symptoms referable to the gastro-intestinal tract in 18 of the 25 cases of "hypoglycemia" which Sippe and Bostock (3) of Brisbane, Australia, reported in 1933. The following is a brief review of the gastro-intestinal symptoms in the 18 cases reported by Sippe and Bostock:

\*Read before the 38th Annual Session of American Gastro-Enterological Association, Atlantic City, New Jersey, June 10, 1935.  
Approved by the Publications' Committee of the Association.

Case 1. Woman, aged 31 years. "Sick feeling accompanied by prostration." Blood sugar 0.062 per cent. Relieved by dieting.

Case 2. Female, aged 26 years. Headaches, relieved by taking food. Blood sugar 0.068 per cent. Symptoms relieved by dieting.

Case 4. Female, aged 35 years. Recurring attacks of severe vomiting, accompanied by "tight feeling around abdomen." Fasting blood sugar 0.080 per cent. Relieved by frequent feedings.

Case 5. Male, aged 33 years. "Feeling as if stomach were gripped by a knot" preceding attacks of unconsciousness, which came on when stomach was empty. Blood sugar 0.079 per cent. Improved by dieting.

Case 7. Male, aged 27 years. Epileptiform convulsions accompanied by intermittent vomiting. Blood sugar 0.077 per cent. Symptoms controlled by dieting.

Case 8. Severe pains in right iliac fossa, accompanied by hysteria. No abdominal rigidity. Pain was relieved by taking food. Blood sugar 0.069 per cent.

Case 9. Female, aged 37 years. Recurring headaches, relieved by taking food; but symptoms accentuated when patient eats "rich" foods. Fasting blood sugar 0.052 per cent. Much improved by dieting.

Case 10. Female, aged 19 years. Sudden severe headaches, followed by dizziness coming on before breakfast. Fasting blood sugar 0.052 per cent. Patient improved, but not completely restored to health, by giving glucose between meals.

Case 11. Male, aged 30 years. Recurring bilious attacks. Gastric discomfort, vomiting, headaches. Fasting blood sugar 0.063 per cent. Patient lost sight of, and results from treatment not known.

Case 13. Female, aged 32 years. History of severe vomiting of pregnancy. Attacks of unconsciousness and vomiting. Not related to meals. Fasting blood sugar at the time of an attack was 0.068 per cent. No attacks since glucose given between meals.

Case 14. Female, aged 37 years. "Forced to eat often to relieve frightful empty feeling." Could work for 2 hours then be "knocked out" and lie down. Could go back to work after eating. Fasting blood sugar 0.077 per cent. Much improved by taking glucose between meals.

Case 15. Female, aged 35 years. Intense hunger, following attacks of weakness, nervousness, and trembling. Relieved by taking food. Fasting blood sugar 0.081 per cent. Symptoms relieved. Can do a full day's work by taking barley sugar between meals.

Case 16. Female, aged 52 years. "Uncanny, hollow feeling" and marked weakness when fasting, relieved by food. Smothering sensation. Fasting blood sugar 0.065 per cent. Improved but not entirely relieved by dieting.

Case 17. Female, aged 36 years. Complaint: "Awakens at 4:00 A. M. every morning with an empty feeling. A headache then commenced, and increased until food was taken when it gradually disappeared. History of "bilious attacks." Fasting blood sugar 0.063 per cent. Frequent feedings. Orange juice and glucose at bedtime. No recurrence of symptoms.

Case 18. Female, aged 25 years. Complaint: Feels tired on awakening, but is relieved by eating breakfast. After working for an hour or two feels faint and has become unconscious on several occasions. Precordial distress, worse after exertion. Fasting blood sugar 0.070 per cent. Result of treatment not given.

Case 21. Female, aged 22 years. Complaint: Emotional depression, nervousness, irritability, epileptiform convulsions. Diagnosis of dementia precox considered. Anorexia, periodic vomiting, with low food intake considered cause of hypoglycemia. Fasting blood sugar 0.082 per cent. Frequent feedings relieved symptoms for a year when patient stopped dieting and symptoms returned.

Case 23. Female, aged 11 years. Complaint: Bilious attacks, vomiting and prostration coming on early in the

morning. Relieved by being given glucose between meals and increased carbohydrate diet. Blood sugar not given.

Case 25. Female, aged 21 years. Complaint: Migrainous headaches once a week. Recurring "bilious vomiting." "Glucose tolerance test showed a low curve." Headaches less frequent and less severe. General condition much improved one year after treatment.

The class of patient as reported by Sippe and Bos-tock is seen frequently by gastro-enterologists. These two Australian clinicians estimate that hypoglycemia is as frequent as the opposite condition, diabetes mellitus, in which hyperglycemia is a manifestation. In their general practice the percentage of hypoglycemia was 0.47 and that of diabetes 0.51.

Moore, O'Ferrell and Mariority (4), of Dublin, Ireland, reported a case of severe hyperinsulinism in which they attributed the hypoglycemia as partly due to "faulty amylaceous digestion":

A woman, aged 27, poorly nourished, was brought into the hospital in semi-conscious state; the following morning she was completely unconscious, limbs rigid, positive bilateral Babinski. Her blood sugar was 0.035 per cent. Ten grams of glucose were injected intravenously. Immediately afterwards she became quite conscious and rational. Had frequent dizzy spells, and always felt better after eating. Examination of her stomach contents showed an achlor-hydia, and repeated examinations of her feces showed much undigested starch. The patient was much improved by diet.

Maxwell (5), an English physician, reports an unusual type of hyperinsulinism:

A female, aged 22, who about an hour after meals had a peculiar "sinking feeling in abdomen as if she were hungry." She then felt faint, and trembled. The patient associated the attacks with eating, and though she felt hungry, was afraid to eat. Her fasting blood sugar was 0.095 per cent. In half an hour after the ingestion of 50 grams of glucose her blood sugar was 0.116, succeeded by a sharp fall to 0.065 at the end of an hour, at the time when her symptoms usually appeared. At the end of two hours her blood sugar had risen to 0.097. The symptoms in this patient were controlled by eating barley sugar or chocolate as soon as the premonitory symptoms appeared. The drop in blood sugar one hour after the ingestion of glucose in a carbohydrate tolerance test is unusual, but several other similar cases of hyperinsulinism have been reported.

A very excellent review of reported cases of hyperinsulinism and hypoglycemia was made by Wauchope (6) in the English "Quarterly Review." Wauchope's article is a valuable contribution to the literature on a subject that seems to be of world interest to the medical profession.

#### FRENCH, GERMAN, AND ITALIAN CASES

Several cases of hyperinsulinism in which there have been gastro-intestinal manifestations have been reported by the French. Labbé (7), reported a case which he called "alimentary hypoglycemia":

A woman, aged 38 years, experienced abdominal pain after meals at which time there were muscular weakness, vertigo and intense hunger, which persisted for half an hour to disappear spontaneously. The patient, thinking that eating brought on the pain, ate sparingly and lost 26 pounds in two years. In this case the ingestion of carbohydrate paradoxically reduced blood sugar when her symptoms appeared, then there was a spontaneous rise in blood sugar and the hypoglycemic symptoms were relieved. Her recorded fasting blood sugar was 0.115 per cent, but in one hour after the ingestion of 50 grams of glucose fell to 0.046 per cent.

A number of other French clinicians have given excellent descriptions of their cases of hyperinsulinism. The interest of the French in hyperinsulinism is shown by the fact that the first book on the subject, "La Hypoglycémie," was written by a Frenchman, Jean Sigwald (8). In this excellent monograph of 300 pages Sigwald reviews the literature on hyperinsulinism and hypoglycemia and reports his studies on experimental hypoglycemic states induced by giving laboratory animals varying doses of insulin.

German clinicians likewise have reported a number of cases of hyperinsulinism in which there were gastrointestinal manifestations; and some of the most important contributions to the literature on this recently recognized disease entity have been published in German medical journals. Indeed, one of the most comprehensive papers that has been published on hyperinsulinism was by Rosenberg (9) of Berlin. Krause (10), another German, made a thorough study of one case in which abdominal pain was associated with recurring attacks of unconsciousness. A diagnosis of an insuloma was made, but operation was refused. Another thoroughly studied case of hyperinsulinism was reported by Frank (11), the pathological report of which was prepared by Tërbrucken. This case, one of multiple islet adenomas, was similar in many respects to the classical case reported by Wilder, Allen and their associates (12) in 1927.

Reports of cases of hyperinsulinism and a number of excellent articles on the subject have appeared in medical journals of many other countries. A few of these cases having gastro-intestinal manifestations will be reviewed.

Theohara and Angelesco (13) of Italy reported the case of a man 27 years of age with a history of 5 years of gradually increasing severity of the symptoms which they described as follows:

"The illness started slowly with epigastric heaviness and eructation after meals, eased by the horizontal position. Later, the patient experienced epigastric emptiness which developed into ravenous hunger before meals, and great agitation—desire to pace the floor, had difficulty to fix his attention on his work—finally unable to add sums. The patient devours his food, the act of eating is a violent impulse. These crises before meals are of variable intensity. If the patient is quiet or isolated, the attacks are milder, at times almost unnoticeable. But as the attacks hinder him at his work, the patient decided to go to the clinic for treatment."

Glycemia: Determined several times in the morning on empty stomach: 0.060; 0.083; 0.075; 0.068 per cent.

Diagnosis: Crises of bulimia with agitation. Moderate hypoglycemia.

Treatment: Regime—meat once a day, vegetables, fruit, milk, predominance of macaronis, rice and pastry. Alkaline bromide, and belladonna 0.01 grain 2-4 times per day.

The patient has not had attacks in the clinic. When he was discharged from the clinic, he continued the belladonna at home, alternating it with suprarenal capsular extract."

Guido Lami (14), another Italian physician, reports an interesting case of "functional hyperinsulinism":

"A macaroni maker, aged 20, gave a history of never having felt a sense of satiety even after heavy meals. His diet consisted largely of macaroni and bread of which he ate 2250 grams a day, but his hunger was never satisfied. When his stomach is empty, he feels cramp like epigastric pains from which he gets relief by eating. Frequently he has to get up at night to eat for the relief of abdominal pain. His fasting blood sugar readings were 0.035 and 0.042 per cent. He also had a severe attack of urticaria.

He was relieved by dieting, peptone 1 gram doses and gluconate of calcium endovenously on alternating days for the relief of the urticaria."

Federico Peco (15), in Santiago de Chili, reported 3 cases of mild hyperinsulinism in a medical journal published in Spain. One patient, a woman aged 23, who had to take food 10 to 12 times a day to prevent attacks of "faintness." Another patient, a merchant, age 42 years, had attacks of unconsciousness during the morning. He had observed that if he ate a good breakfast the attacks did not occur. The attacks had been coming on almost daily for a year. "An alimentary regimen rich in carbohydrates was sufficient to make the crises disappear." Peco's third case was a writer, age 26 years, who had observed that following an attack of "flu" he had a faint, weak feeling a few minutes before eating, especially if his meals were delayed. He became unconscious at a dance. His friends believed him drunk and carried him home. After taking a cup of sweetened coffee, he felt perfectly well and assured his friends that he had not been drinking. The patient had no recurrence of symptoms on a diet rich in carbohydrates and with the use of epinephrine.

Maranos (16) called attention to the fact that acidosis may occur in hypoglycemia as well as in hyperglycemia (diabetes mellitus). The gastro-intestinal symptoms of acidosis which he describes as having occurred in his patients with hypoglycemia are loss of appetite, vomiting and diarrhea. Cammidge likewise called attention to the fact that acetone, diacetic acid and glycosuria may be found in patients who have hypoglycemia.

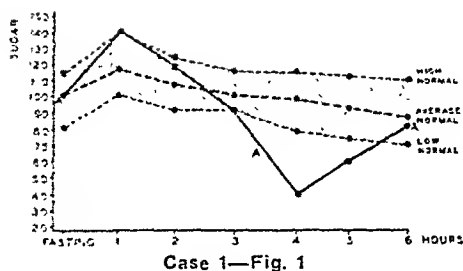
#### RUSSIAN CASES

It is interesting to note that while cases of hyperinsulinism have been reported in nearly all the European nations, and a number of cases have been reported in Central and South America, the only country in the world, except the United States (about 40 cases) and Canada (1 case), in which surgery has been resorted to for the relief of hyperinsulinism has been Russia. Federoff (17) in Metchinkoff's Clinic in Leningrad has performed one partial resection of the pancreas—the patient, an obese boy 16 years of age died—and an exploratory operation, finding in the latter case an inoperable tumor of the caudal end of the pancreas. It is also interesting to note in studying the literature on hyperinsulinism in the medical journals of many countries that all over the world progressive physicians are practicing the same kind of scientific medicine as in the United States. It is pleasing to note that physicians in every country in reporting cases of, or in reviewing the literature on, hyperinsulinism are familiar with the work that has been done on this recently recognized disease entity by American clinicians.

One of the Russian cases operated on by Federoff should be of interest to gastro-enterologists:

A physician, aged 40. The earliest symptom was pain in the region of the stomach; and like a number of American cases of hyperinsulinism, it was first diagnosed ulcer of the stomach. An operation was performed but no ulcer was found. There is no record of an examination of the pancreas at the first operation. A gastro-enterostomy and an appendectomy were performed with only temporary benefit. The abdominal pain continued and in addition there were attacks of fainting preceded by numbness of the tongue and profuse sweating. The attacks recurred generally before meals and were relieved by eating. The patient found that the attacks could be prevented by eating





Case 1—Fig. 1

sugar, and he always carried a lump of sugar to prevent or relieve the attacks. The pains increased in intensity and there was a sense of heaviness in the stomach after meals. The blood sugar rose to 0.282 per cent in one-half hour after taking glucose, and then fell rapidly to 0.055 per cent when the patient complained of a sensation of suffocation, then sweating and trembling. In another half hour the patient became comatose, when the blood sugar level was 0.027 per cent. After administering 15 grams of glucose intravenously, consciousness returned when the blood sugar had risen to 0.065 per cent. An exploratory laparotomy revealed an enlarged hard pancreas with a tumor of the caudal end reaching to the right lobe of the liver. The report does not state how long the patient lived after the operation, but adds that the autopsy showed a large tumor of the tail of the pancreas, cancerous nodes in the omentum and an enlarged liver, presumably from metastases.

#### ABDOMINAL SYMPTOMS IN AUTHOR'S REPORTED CASES

It is not possible to review the literature of all of the many cases of hyperinsulinism in which there were gastro-intestinal manifestations as reported by American clinicians; but brief reports of a few personal cases, in which there have been abdominal symptoms, will present some of the problems incident to the diagnosis and treatment of hyperinsulinism that may interest gastro-enterologists.

In the October (1934) number of this Journal in an article on "Clinical Types of Hyperinsulinism" (18) I reported 15 cases. A brief review of some of the cases reported in that article will bring out some of the protean abdominal symptoms of hyperinsulinism:

Case 1. Hypoglycemic symptoms, i.e., extreme hunger, weakness, nervousness and profuse perspiration in addition to recurring attacks of abdominal pains. Undoubtedly chronic cholecystitis (non-visualization of the gall bladder Graham-Cole test). Tenderness over pancreas, chronic pancreatitis suspected. Low blood sugar, 0.050 per cent. Hyperinsulinism symptoms controlled by dieting, but has occasional attacks referable to the gall bladder and pancreas. Operation refused.

Case 2. A case of proved duodenal ulcer in addition to hypoglycemic symptoms. Blood sugar 0.060 per cent. Both the ulcer and the hyperinsulinism were relieved promptly by dieting. No symptoms for 3 years.

Case 3. Hyperinsulinism with ulcer symptoms. Sent in with diagnosis of duodenal ulcer because of abdominal discomfort between meals, relieved by taking food. No filling defect in duodenum on X-ray examination. Achlorhydria. Blood sugar, 0.060 per cent, 4, 5, and 6 hours

Fig. 1. A. Blood sugar curve in dextrose tolerance test. At the end of 4 hours when blood sugar level fell to 0.040 per cent, he became very dizzy and weak, fearing fainting. Pulse rate, 40. He felt better after lying down, and his blood sugar rose within an hour to 0.066 per cent, in 2 hours to 0.092 per cent when symptoms were relieved without taking food.

after taking food. Symptoms relieved by taking food between meals and the use of dilute hydrochloric acid (1 oz. or 4 c.c.) mixed with milk at meals and 3 hours after meals.

Case 4. Paroxysmal tachycardia with pains and soreness in the upper part of abdomen. Normal fasting blood sugar (0.100 per cent); but in one attack when pulse was about 200 she complained of "gas on stomach pressing around heart"; her blood sugar was 0.056 per cent. Relieved in a few minutes from taking 50 grms of glucose. A dextrose tolerance test showed low readings, 0.060 per cent at the end of 5 hours. Has been much improved on a low carbohydrate, high fat diet with feedings between meals, though she has had an occasional paroxysm of tachycardia.

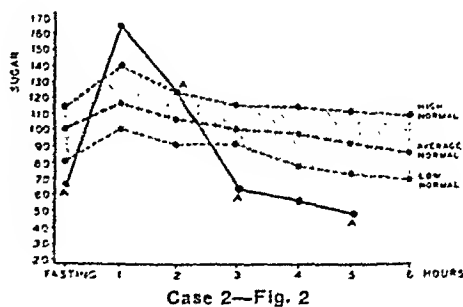
Case 5. Hysterical attacks in a woman 56 years of age, who complained of hunger, numbness, tachycardia, (gas in stomach pressing on heart), gaseous eructations 2 or 3 hours after breakfast. Insomnia—gets up to eat several times a night. In her dextrose tolerance test at the end of 5 hours when her blood sugar fell to 0.048 per cent, she had a hysterical attack, which was relieved by taking a glass of malted milk. Symptoms prevented by dietary management and patient was in good health when last heard from a year after having begun treatment.

Case 6. Hyperinsulinism and neuro-circulatory asthenia in a woman who complained of nervousness and weakness between meals. In 1923 she had symptoms of a duodenal ulcer and was improved by rest and ulcer diet. Her abdominal discomfort and weakness began 2 hours after meals when her blood sugar fell to 0.070 per cent. Five hours after a dextrose tolerance test her blood sugar was 0.048 per cent. Frequent feedings of a low carbohydrate, high fat diet relieved her.

Case 7. Hyperinsulinism induced by reducing diet. This case illustrates the dangers of reducing without the direction of a physician. A woman reduced 75 pounds in a year and became very irritable, nervous, emotionally unstable, and actually psychotic, having had delusions of persecution. She also had upper abdominal pains. She was relieved by frequent feedings. No symptoms in 3 years.

Case 8. Hyperinsulinism and recurring attacks of abdominal pains and unconsciousness. Referred with diagnosis of gall stones or peptic ulcer. History of taking 15 or 20 glasses of coca-cola a day. Had been operated upon for appendicitis following an attack. Low glucose tolerance curve, 0.070 per cent after 2 hours and at 6 and 7 hours blood sugar was 0.050 per cent. On a low carbohydrate, high fat diet he has had no abdominal pain or unconscious attack in 3 years.

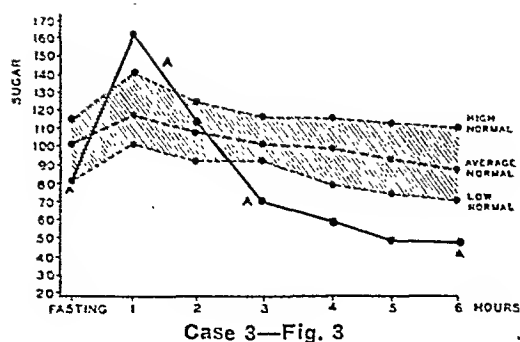
Case 10. Dysinsulinism associated with abdominal pain and tenderness in upper part of abdomen, nausea, vomiting and a low grade fever, followed pelvic infection 6 months



Case 2—Fig. 2

Fig. 2. A. Dextrose tolerance curve. Note: When blood sugar dropped to 0.060 per cent, she was so weak that she had to go to bed. She complained of palpitation and tachycardia. Test was continued for one hour longer and at the end of five hours blood sugar was 0.050 per cent when the tolerance test was discontinued. She was relieved in a few minutes by taking a glass of malted milk.





previously. Fasting blood sugar 0.062 per cent, at which time her pulse rate was 108, and she was quite uncomfortable. She received almost immediate relief and her pulse rate fell to 72 from taking 100 grams of dextrose. Her dextrose tolerance curve was distinctly diabetic, having risen to 0.200 per cent in 3 hours after the ingestion of the dextrose. A diagnosis of sub-acute pancreatitis was made. She was improved by rest and frequent feedings.

Case 11. Dysinsulinism associated with recurring attacks of pain and tenderness over the pancreas, nausea and vomiting. Appendix had been removed 2 years before without relief of symptoms. Had "spells" of weakness and fainting before breakfast and when stomach is empty, relieved by eating. Her fasting blood sugar was 0.060 per cent. One hour after dextrose it rose to 0.200 per cent and then fell to 0.050 per cent 5 hours later. Dietary management for 5 months gave no relief. Resection of the pancreas resulted in a clinical cure—no symptoms in more than a year.

Case 12. Hyperinsulinism and epilepsy apparently resulting from trauma of the pancreas. Following an abdominal injury, after a month in bed suffering from pain, nausea and vomiting, a high school girl began having epileptic attacks. The convulsions now occur only during menstruation. In a dextrose tolerance test when her blood sugar fell to 0.050 per cent, she had a light epileptic convulsion. She had no attacks for several months, but gave up dieting and her attacks have recurred.

Case 13. Narcolepsy and recurring attacks of abdominal pain. Appendix had been removed without relief a year before. Fasting blood sugar was 0.050 per cent. Hypoglycemic symptoms, including abdominal pain, were controlled while in the hospital, but he could not carry out diet properly at home, and the symptoms recurred. He therefore was operated upon with complete relief of symptoms for 3 years. Glucose tolerance test 2 years after operation was normal.

#### ADDITIONAL CASES WITH GASTRO-INTESTINAL SYMPTOMS

The following reports of additional cases hitherto unpublished present symptoms and syndromes that may be involved in making a diagnosis of hyperinsulinism:

*Hyperinsulinism and "Nervous Indigestion."* Case No. 1. August 14, 1934. Formerly merchant, now on government relief roll. Age 44. Height 6 feet. Weight 154 pounds.

*Symptoms:* Attacks of gaseous eructations, dyspnoea, nervousness, twitching of muscles of hands and face.

Fig. 4. Dextrose tolerance test. Note: At the end of 4 hours when the patient's blood sugar was 0.060 per cent, he complained of hunger and weakness and felt as if he would faint. He was so uncomfortable that the test was concluded at the end of 4 hours. Was given a glass of malted milk and obtained relief from symptoms in a few minutes.

Fig. 3. A. Dextrose tolerance test.

When hungry he has pains in abdomen, is nauseated and sometimes vomits. Feels better after eating. If he misses a meal, he becomes weak and prostrated. Constipation. At times his mind becomes "inactive" so that he cannot work. Physical examination, negative. About 3 hours after breakfast, while waiting in the clinic office for examination, he became very weak, complained of "gas on stomach," and hunger. His blood sugar at that time was 0.058 per cent. He was relieved in a few minutes from taking a glass of malted milk.

*Treatment:* On a low fat, high carbohydrate diet with food 3, 4, and 5 hours after meals has been quite comfortable and able to do some work. Improvement has continued for 8 months, though on account of financial conditions he has not been able to get proper food at all times.

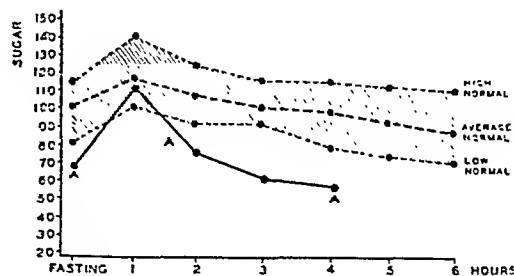
*Comment:* This patient had been examined by a number of physicians, some of whom had told him there was nothing the matter with him, and others diagnosed his case as hysteria. An over-dose of insulin (induced hyperinsulinism) in one of our patients caused a drop in pulse rate to 40 when his blood sugar fell to 0.055 per cent. Since this man's pulse rate dropped to 40 when his blood sugar fell to 0.040 per cent, it appears that spontaneous hyperinsulinism may be one of the causes of bradycardia.

*Hyperinsulinism, Abdominal Pains, Hunger Spells and Psycho-neurasthenia.* Case No. 2. April 18, 1932. Housewife. Age 38. Height, 5 feet 3 inches. Weight, 148 pounds.

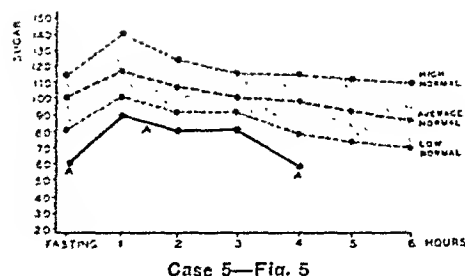
*Symptoms:* Fatiguability and weakness; becomes exhausted from slightest exertion. Nervousness, trembling, profuse perspiration—"hunger spells"—relieved by taking glass of milk or other food. Abdominal pains and backache. Constipation. Symptoms more pronounced during menstruation. Twenty pounds underweight. Occasional trace of sugar in urine. She was given barium with malted milk for gastro-intestinal series. When she returned for the six hour examination, she was very weak, nervous and pale. On fluoroscopic examination her heart was observed to be beating rapidly, 96 per minute. A blood sugar at that time was 0.050 per cent. Gastric analysis showed total acidity of 30 and free hydrochloric acid, 20. Blood pressure 126 over 82. Her basal metabolic rate was plus 12 per cent. Wassermann, negative.

*Treatment:* Was very much improved by rest and frequent feedings. Marked tendency to obesity. Is regarded as a potential diabetic.

*Comment:* This patient came for relief of symptoms which she attributed to "indigestion." The hypoglycemic symptoms were so pronounced during an X-ray gastro-intestinal series, six hours after the barium and malted milk, that a blood sugar test was made and found to be 0.050 per cent. She was then given a glass of malted milk, and the nervousness and weakness subsided in a few minutes. The next day she was given a dextrose tolerance test which con-



Case 4—Fig. 4



Case 5—Fig. 5

firmed the diagnosis of hyperinsulinism. We have had a number of other cases in which during the fasting period of a gastro-intestinal X-ray study the patients complained of weakness, nervousness and tachycardia five or six hours after the morning barium and malted milk meal. Blood sugar tests proved that the symptoms were due to hypoglycemia. If gastro-enterologists and roentgenologists will question patients regarding their suggestive symptoms during the X-ray examination, they may find the clue for the diagnosis and treatment that will relieve the patient.

**Hyperinsulinism, Ulcer Symptoms, Nervousness and Insomnia.** Case No. 3. January 1, 1927. Rural mail carrier. Age 26. Height, 5 feet 8½ inches. Weight, 153½ pounds.

**Symptoms:** Heartburn, eructations of gas and sour liquids. Abdominal pain occurring 3 hours after eating and relieved by food. Nervousness. Gastric analysis showed total acidity 25, free hydrochloric acid 10. No occult blood in stools. X-ray examination showed orthotonic stomach with no filling defect but slightly irregular duodenal cap. No residue in stomach six hours after barium meal. Case considered suspicious at that time of duodenal ulcer and hyperinsulinism was not suspected. Patient returned on May 24, 1932, with much the same symptoms but complained particularly of nervousness and restlessness. Dreaded for night to come because of insomnia. Tires easily and complained of weakness and trembling at times.

**Treatment:** On a moderately low carbohydrate, moderately high fat diet with frequent feedings during the day, food at bedtime and every 3 hours when awake at night the patient's symptoms were relieved.

**Comment:** In this case the ulcer symptoms were pronounced and there was a filling defect in the duodenum before the hypoglycemic symptoms were pronounced. The irregular duodenal cap probably was not due to a lesion but to a spasticity probably from the nervous irritability resulting from the hypoglycemia. It is difficult to differentiate between hyperinsulinism and duodenal ulcer from the symptoms alone. A hypoglycemic curve as in this case may decide the diagnosis but it should be remembered that patients may have duodenal ulcer and hyperinsulinism.

**Hyperinsulinism Associated with Gastric Neurosis and Syphilis.** Case No. 4. March 23, 1932. Baker. Age 44. Height, 5 feet 7 inches. Weight, 116 pounds.

**Symptoms:** Frequent attacks, 20 or more in a month, of dizziness, mental lapses and tight feeling in chest, smothering sensation, difficult breathing, palpitation, gaseous distention, "gns pressing on heart," abdominal discomfort. Attacks usually occur between 11 and 12 o'clock in the morning and at about 5 o'clock in afternoons. Feels better after eating. Gastric analysis showed total acidity of 50, free hydrochloric acid of 40. X-ray showed a hypo-

Fig. 5. Dextrose tolerance test.

tonic stomach with no filling defect but the duodenum did not fill regularly and there was 15 per cent residue in the stomach 6 hours after the barium meal. Routine blood Wassermann was 4 plus. A repeated test the following day was also 4 plus and the Kahn test was positive. He denied an initial lesion or any history of syphilis. Fasting blood sugar was 0.080 per cent. Basal metabolic rate was plus 3. Blood pressure 112 systolic over 65 diastolic.

**Treatment:** Patient was placed on a low fat, high carbohydrate diet with frequent feedings between meals and when awake at night. Was given arsphenamine and bismuth (Kidder-Moore treatment for syphilis) by his home physician. The hypoglycemic symptoms were relieved almost immediately by dieting and 2 years later he states that he had had no recurrences of his hypoglycemic symptoms.

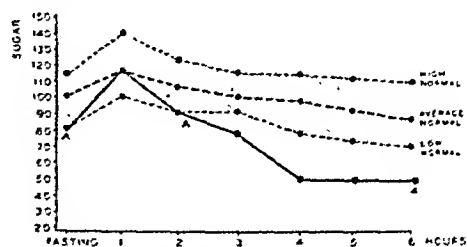
**Comment:** In this case a routine Wassermann in a patient without luetic history was positive. The diagnosis of syphilis was confirmed by repeated Wassermann and Kahn tests. The fasting blood sugar was the low normal but the symptoms were so suggestive of hypoglycemia that a glucose tolerance test was made, and it showed unquestionably hypoglycemia. The fact that the gastric and cardiac neuroses were relieved by dieting seemed to prove that the syphilis had nothing to do with the hypoglycemia.

**Hyperinsulinism and Psycho-neurasthenia with Gastric Symptoms.** Case No. 5. February 16, 1932. Housewife. Age 32. Height, 5 feet 5 inches. Weight, 132 pounds.

**Symptoms:** Duration 8 years. Five years ago was in bed for almost a year because of varied gastro-intestinal and nervous symptoms. Has no energy. Dreads work. Excessive hunger associated with nervousness and weakness. Feels normal after meals. Eats frequently in order to work. Has had varied digestive symptoms including abdominal pains, choking sensation, sour stomach. Symptoms more pronounced from work like sewing.

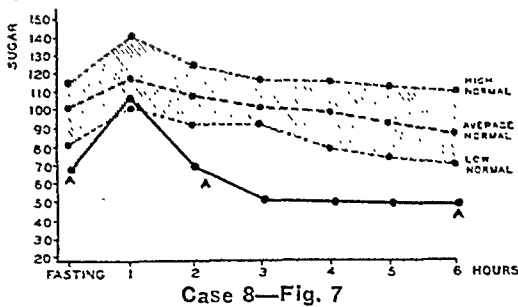
**Treatment:** Greatly improved on low carbohydrate diet with orange juice or tomato juice every hour between meals and frequent rest periods during the day. Fasting blood sugar 0.068 per cent, January 26, 1933, after one year's dieting; and in June, 1935, fasting blood sugar was 0.075 per cent.

**Comment:** This is a pronounced case of psycho-neurasthenia with gastric neuroses. She was almost a confirmed invalid when the treatment was begun. She has had 3 years of comparative comfort on a diet consisting largely of fruits, 5 and 10 per cent vegetables, meat once a day and a slice of bread with meals, with frequent feedings intended to maintain blood sugar levels within normal limits. Rest also played an important part in keeping this patient comfortable. In making dextrose tolerance tests we have observed several patients when the blood sugar level fell to 0.060 per cent or lower, hypoglycemic symptoms developed that subsided on lying down.



Case 6—Fig. 6

Fig. 6. A. Blood sugar curve in dextrose tolerance test.



*Hyperinsulinism and Psychasthenia.* Case No. 6. December 29, 1934. Teacher, unmarried. Age 54. Height, 5 feet 8 inches. Weight, 139 pounds.

*Symptoms:* Extreme fatigability. Feels well on arising but 2 or 3 hours after breakfast becomes extremely tired. Feels better after luncheon but about 3 P. M. becomes exhausted mentally and physically. Feels better after supper but is unable to concentrate her mind to read or study at night. Has a heavy uncomfortable feeling in abdomen, sometimes actual pain, in the upper left quadrant 2 or 3 hours after meals. She was referred because of gastric symptoms.

*Treatment and Results:* A low carbohydrate, high fat diet with feedings every 2 hours between meals and until bedtime gave almost immediate relief. She has had no gastric or psychasthenic symptoms in 5 months. She says that she feels like a different person.

*Comment:* The mental depression, abdominal discomfort and inability to work from 3 hours after meals and until after the next meal; and the euphoria for 3 hours after meals, when blood sugar levels are within the normal range parallel one of Powell's cases of a child who, when her blood sugar levels were within the normal range, learned readily, and for the 2 or 3 hours before noon meals and in the afternoon when the child could not learn the blood sugars were below 0.060 per cent. The dramatic results in this case of simple dieting has transformed a teacher into an efficient happy woman, whereas she had been miserable and in failing health, as she thought, for a year previous.

*Hyperinsulinism, Headaches and Gall Bladder Symptoms.* Case No. 7. July 15, 1932. Housewife. Age 36. Height, 5 feet 6 inches. Weight, 142 pounds.

*Symptoms:* Pain in epigastrium, extending to the left side of the abdomen, and weak spells about 11 A. M. and 4 or 5 P. M. and at night about 1 or 2 A. M. Discomfort and pain continues and is unable to get back to sleep for the rest of the night. Also complains of pains and soreness in shoulders and arms. The pain is not relieved by eating—feels better when stomach is empty and pain is worse from eating solid food. Eructates food after meals and occasionally vomits. She feels well for weeks at the time and usually has the spells in the spring and fall. Fatiguability, irregular menstruation, nervous headaches, more frequent during menstruation. Her case had been diagnosed as gall bladder trouble and an operation had been advised by her local surgeon. Her brother had been operated on a few weeks before for gall bladder trouble and died following the operation. The physical examination was practically negative except the general tenderness

Fig. 7. Dextrose tolerance curve.

over the abdomen, more in right and left lower quadrants. Her urine, blood and feces were normal. Wassermann negative, basal metabolic rate plus 1.9 per cent. Gastric analysis showed total acidity of 110, free hydrochloric acid 70 one hour after the Ewald test meal. The X-ray showed a hypotonic stomach, no filling defects in stomach or duodenum. Duodenum slow in emptying. Graham-Cole test showed normal gall bladder which was slow in emptying.

*Blood sugar findings:* August 15, 1932, 10 A. M., 0.060 per cent and 4 P. M. 0.060 per cent. The following morning her fasting blood sugar at 8:30 was 0.060 per cent and at 10 A. M., 0.055 per cent. A dextrose tolerance test was not made because she could not remain in Birmingham long enough.

*Treatment:* On a relatively low carbohydrate, high fat diet her headaches, abdominal pains and other symptoms subsided. Letters from her stated that she was very much improved.

*Comment:* This patient came to this Clinic after diagnosis had been made of gall bladder disease and an operation advised. Her brother had been operated upon for gall bladder trouble a few weeks previously and had died following the operation. She came to us for advice as to whether or not she should have the operation. The Graham-Cole test showed a practically normal gall bladder that emptied slowly. There was hyperchlorhydria but no evidence of ulcer. Apparently her symptoms were caused by hypoglycemia, because she was relieved by a low carbohydrate, high fat diet with frequent feedings. The periodicity of symptoms, with euphoria for weeks at a time, followed by periods in which her symptoms came on at about 11 A. M., 4 P. M. and 5 P. M. and 1 or 2 P. M. suggested an ulcer. The patient was not placed on an ulcer diet but was given frequent feedings and the symptoms subsided. Apparently her pain and attacks of weakness were due to the hypoglycemia of hyperinsulinism.

*Abdominal Pain in Hyperinsulinism with Glycosuria. Potential Diabetic.* Case No. 8. March 3, 1933. Student nurse. Age, 22. Height, 5 feet 5 inches. Weight, 135 pounds. (Referred because sugar found in urine).

*Symptoms:* Weakness, nervousness, irritability, dizziness ("staggers") and mental lapses 3 or 4 hours after meals. Trembles, perspires, has difficult breathing, and becomes very pale in attacks. Relieved in a few minutes after eating. Abdominal pains between meals and at night. Relieved by taking orange juice or other food. Had similar but more severe attacks in 1928 when 3 or 4 times she fell and became unconscious when stomach was empty. Is excessively hungry before meals. When she sees food and has to wait her turn in hospital cafeteria, she becomes very weak, and on one occasion became unconscious.

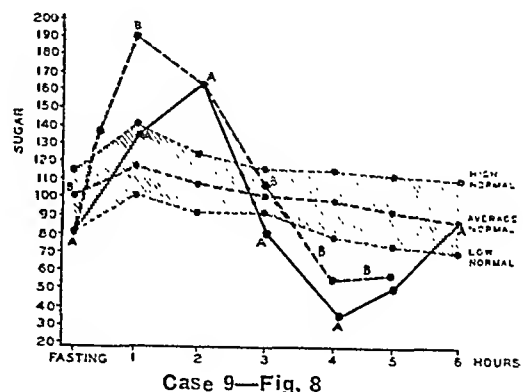
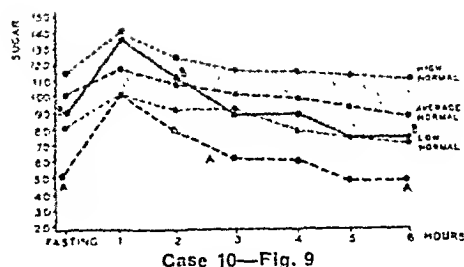


Fig. 8. A. Dextrose tolerance test May 22, 1935, (Folin-Wu Method). At the end of 4 hours when blood sugar was 0.035 per cent, had typical insulin reaction—prostration, marked weakness, nervousness, trembling, sweating and extreme hunger—asked that test be stopped and food given him, but agreed to continue it. After rest and dozing in a chair, in 1 hour blood sugar had risen to 0.050 per cent and in 2 hours to 0.100 per cent—2 plus sugar in urine 2 hours after luncheon.

Case 9—Fig. 8



Case 10—Fig. 9

**Treatment:** On a weighted and measured diet, 120 Ch., 75 P., and 180 F., with orange juice or tomato juice and cream every 1 or 2 hours between meals and until bedtime all her symptoms were relieved. She has had no symptoms for 2 years. The fats were reduced as symptoms subsided.

**Comment:** In spite of admonitions against overeating this patient is becoming obese. She is regarded as a potential diabetic. Glycosuria is seen frequently in hyperinsulinism. Twenty-five per cent of Cambridge's 200 cases of "chronic hypoglycemia" had glycosuria. May not the so called "low renal threshold" be of pancreatic origin?

**Dysinsulinism with Abdominal Pain and Diarrhoea.** Case No. 9. May 22, 1935. Physician. Age, 42. Height, 5 feet 3½ inches. Weight, 146 pounds.

**Symptoms:** About 3 hours after eating becomes faint, weak, restless, irritable, has a sensation of extreme hunger, trembles and is in profuse perspiration. Has aching and soreness in the abdomen ("low grade colic"). Obtains immediate relief from eating. If food is delayed 5 or 6 hours, he has almost total collapse, but obtains relief very quickly after eating. Symptoms exaggerated after taking soluble carbohydrates. Has "hungry pain," a feeling of pylorospasm, on awakening in the morning, from which he gets immediate relief by eating. Extreme fatigability. Has abdominal cramps and diarrhoea after the ingestion of fats. Glycosuria in afternoons but none in mornings. Has precordial pain and dyspnoea on exertion at anytime. Symptoms have grown progressively worse. Has been in hospital twice—once for 5 weeks and at another time for 1 week. Is improved by rest, but symptoms recur on returning to work.

**B. Dextrose tolerance test (Schaffee-Harman-Samogyi Method)** Barnes Hospital, February 20, 1935.

**Treatment:** Patient hospitalized and is comfortable on a diet of 120 C., 60 P., 120 F. with food every 2 hours between meals. Because of the rapid course and increasing severity in symptoms so that this patient is a semi-invalid, an adenoma of the pancreas is suspected. An operation will be advised if improvement does not continue.

**Recurring Attacks of Headache, Vomiting and Unconsciousness Due to Brain Tumor Involving Hypophysis.** Case No. 10. September 27, 1934. Teacher. Age, 39. Height, 5 feet 8 inches. Weight, 138 pounds.

**Symptoms:** Following an attack of what was called flu, patient had attacks of drowsiness and slurring of speech late in the afternoons. Two or 3 months later he began having attacks of headaches, vomiting and unconsciousness during which time he was very restless but had no convulsions. Intervals of euphoria between attacks. Physical Examination: Negative. Blood count, normal. Wassermann, negative. Ophthalmoscopic examination revealed choked discs in the right and left eye with few small hemorrhages around and over the discs. Vision normal on June 25, 1934. In October, 1934, vision was 25—50 plus. Stereoscopic film of skull showed marked broadening of the sella tursica. Diagnosis of brain tumor involving the hypophysis was made.

**Comment:** Even though this patient had a brain tumor involving the hypophysis, on low carbohydrate,

Fig. 9. A. Dextrose tolerance test September 28, 1934. B. Dextrose tolerance test 3 months after being on low carbohydrate, high fat diet.

high fat diet with frequent feedings between meals, his hypoglycemic symptoms were relieved temporarily. After a few weeks his headaches became more intense and patient was in stupor at times. Operation for brain tumor urged, but refused. He died at his home in the country. No autopsy; but the choked discs, enlarged sella tursica shown in skull picture, the headaches, vomiting and unconscious attacks make certain the diagnosis of a tumor involving the hypophysis.

### OBESITY AND HYPERINSULINISM

Wilder (19), who with his associates, Allen and Robertson (12), reported the first case of convulsions and unconsciousness due to hyperinsulinism, and who proved the pathological basis for this new disease entity, in a valuable summary of the present knowledge of hyperinsulinism states that gastro-intestinal symptoms are "fairly frequent"; and he mentions "flatulency, epigastric burning and constipation. Two patients were operated on for undiscovered ulcers. One had gall stones."

Wilder mentions Winans' (20) two cases of obesity in which the first symptom of hyperinsulinism followed efforts at reduction of weight by dieting. My first case of dysinsulinism reported in 1924 was an obese woman who had diabetes and her first hypoglycemic symptoms followed marked restriction in her food to control the diabetes. My first 2 cases reported in 1923 (21) was in an article on the etiology of diabetes in which the suggestion was made that the hunger and the overeating associated with hyperinsulinism may be the cause of the obesity which is so frequent in diabetes. Wilder cites Winans as sharing Falta's opinion that "overstimulation of the pancreas may lead primarily to obesity and later to diabetes." Wilder also mentions that "in several instances a diabetic state of metabolism has come first and hypoglycemia later," mentioning the case of "a woman 40 years of age who formerly required large doses of insulin to control glycosuria and now presents the clinical picture of hyperinsulinism, with blood sugar as low as 40 mg. for each 100 c.c."

### HUNGER IN HYPERINSULINISM

The hunger and the abdominal discomfort that are frequently but not invariably associated with hyperinsulinism, induced from overdoses of insulin or that occurs spontaneously in non-diabetics in some cases, may be accounted for by the gastric peristalsis which usually accompanies a falling blood sugar—not necessarily associated with hypoglycemia (John) (22). Graham (23) states that in hyperinsulinism the sensation of hunger may be extreme or agonizing. Graham cites Carlson and his associates as having shown that "hypoglycemia is associated with violent contractions of the stomach." Wilder (19) says that "a feeling of intense hunger is usually but not always present." He cites Quigley, Johnson and Solomon (24) as accounting for the hunger in hyperinsulinism by excessive gastric peristalsis, but adds that Heinz and Palmer (25) have found that gastric mobility from hypoglycemia is frequently absent in man. Wilder also cites LaBarre and Destree (26) as having found that "hypoglycemia of about 75 mg. in each 100 c.c. provoked gastric contrac-

tions, whereas with still lower depressions, about 45 mgs. in each 100 c.c. gastric atony developed." My clinical experience seems to confirm the last statement, because in the mild type of hyperinsulinism, with blood sugar readings from 0.075 to 0.050 per cent, the hunger and gastric distress are more severe than in the most severe cases in which there are lower blood sugar readings. In the latter cases, as Wilder (19) has pointed out, occasionally there has been a disgust for food, and sometimes actual sitophobia, because the patient erroneously regards the attacks as being due to eating.

#### THE VALUE OF ROUTINE BLOOD SUGAR STUDIES ON GASTRO-INTESTINAL PATIENTS

Routine Wassermanns and routine examination of the urine and feces are accepted procedures in the examination of every patient who consults a gastro-enterologist. The high incidence of hyperinsulinism, or chronic hypoglycemia, in gastro-intestinal patients as reported by clinicians all over the world indicates that routine blood sugar studies on patients who complain of symptoms referable to gastro-intestinal and other abdominal diseases may in some cases give the gastro-enterologist information that will be helpful in prescribing diets and other remedial measures which may relieve or cure the sufferer of his complaints.

This new disease entity may simulate peptic ulcer, irritable colon, cholecystitis, appendicitis, pancreatitis, and particularly the group of cases now classified as neuroses of the stomach, intestines and other abdominal viscera. Certainly in some cases in order to differentiate between gastro-intestinal, gall bladder diseases, or other intra-abdominal disease or functional disturbances and hyperinsulinism, blood studies are necessary. Even when there is a positive diagnosis of an intra-abdominal lesion, hyperinsulinism may exist as a complicating factor which may be the cause of some of the most disagreeable symptoms of which the patient complains.

It adds but little to the laboratory work of the gastro-enterologist to make routine blood sugar studies on every patient whom he examines. The technician can get enough blood for a blood sugar determination when a venepuncture is made for the Wassermann and Kahn tests. It is best to obtain such specimens before breakfast on the second day of the examination; and if indicated, enough additional blood may be drawn from the vein for calcium, non-protein nitrogen, urea, and creatinin determinations. Cammidge (2) says that "accurate determinations of blood sugar may be made in less than half an hour by the micro-method from a finger prick."

A low fasting blood sugar suggests, but is not proof of, hyperinsulinism, because hypoglycemia may also be due to dysfunction of the liver or the pituitary, thyroid and adrenal glands. It, therefore, is necessary to exclude disease, or disorder, of the liver and the endocrine glands before assuming that the hypoglycemia found in any case is due to the hyperactivity of the internal secretory glands (islands of Langerhans) of the pancreas.

The diagnosis of hyperinsulinism may be suspected, or even assumed, in the patient who complains of weakness, nervousness, anxiety, trembling, sweating and inability to concentrate on work one or two hours before meals; symptoms that are relieved by eating

only to recur when the stomach is empty; but the diagnosis is confirmed only by finding hypoglycemia at the time when the symptoms occur, i.e., the fourth, fifth, or sixth hour of a glucose tolerance test. Occasional cases have been observed when low blood sugar readings are found in the second and third hours of the glucose tolerance tests, but there may be no abnormally low blood sugar readings until the fifth or sixth hours. Four hours is sufficiently long to carry out a glucose tolerance test for diabetes; but in a suspected case of hyperinsulinism, the tests should be made hourly for six hours. Sometimes the hypoglycemic symptoms may be reproduced during the glucose tolerance test. If so, in order to relieve the symptoms, it may be best to give the patient food.

A low fasting blood sugar obtained in the routine examination of a patient may be the clue for making a six hour glucose tolerance test that will prove hypoglycemia as the cause of some or all the gastro-intestinal symptoms of which the patient complains. It, therefore, seems that routine fasting blood sugars are of as much value in the diagnosis of gastro-intestinal cases as are Wassermanns or the routine examination of the urine and feces.

Already gastro-enterologists, more than other medical specialists, are finding cases of hyperinsulinism; and since the mild and moderately severe types of hyperinsulinism usually can be relieved by dietary management, it is important to use routinely a simple laboratory procedure that will remove many cases from the realm of the make-shift diagnosis of gastro-intestinal neuroses to the domain of an accurately determined and well known disease entity that usually is amenable to treatment.

#### CONCLUSIONS

1. Reports of cases of hyperinsulinism by clinicians in many countries show that the gastro-intestinal manifestations of this new disease entity are protean and important.

2. Abdominal pain between meals and during attacks of unconsciousness has been pronounced in several reported cases so that a number of hyperinsulinism patients have been subjected to needless operations in which an erroneous diagnosis of appendicitis, duodenal ulcer or cholecystitis had been made.

3. Hyperinsulinism has occurred frequently in patients who have had proved abdominal lesions, including duodenal ulcer, cholecystitis, pancreatitis and tumors of the islands of Langerhans.

4. Dietary management usually controls, or cures, hyperinsulinism in intelligent, cooperative patients.

5. Resections of the pancreas and the removal of insulomas have produced clinical cures in hyperinsulinism patients who were not relieved by dietary management.

6. Fasting blood sugar studies, dextrose tolerance tests, and glycemia determinations during attacks in gastro-intestinal patients, particularly those who think they have "nervous indigestion," may reveal hypoglycemia as the underlying factor in many cases.

#### REFERENCES

1. Cammidge, P. J.: Chronic hypoglycemia. *Brit. Med. Jr.*, 1930, 1:818-822.
2. Cammidge, P. J.: Chronic hypoglycemia as operative risk. *Brit. Jour. Urol.*, 2:109-112, June, 1930.
3. Sippe, C., and Bostock, J.: Hypoglycemia: Survey and account of 25 cases. *Med. Jour. Australia*, 1933, 1:207-218.



4. Moore, H.: O'Farrell, W. R.; Malley, L. K., and Moriarty, M. A.: Acute spontaneous hypoglycemia. *Brit. Med. Jour.*, 1931, 2:537-540.
5. Maxwell, J.: Spontaneous hypoglycemia: case. *St. Barth. Hospital Jour.*, 40:105-107, 1933.
6. Wauchope: Reported cases of hyperinsulinism and hypoglycemia. *English Quarterly Review*.
7. Labbe, M.; Boulin, R., and Petresco, M.: Alimentary hypoglycemia, with report of unusual case. *Bull. et mèm. Soc. Med. d. Hop. de Paris*, 48:181-186, Feb. 15, 1932.
8. Sigwald, Jean: (a) L'hypoglycémie, 1932, Gaston Doin, Paris. (b) Les hypoglycémies spontanées, *Paris Med.*, 1932, 2:321-332.
9. Rosenberg, M.: Über arteriellen und spontanen Hyperinsulinismus. *Klin. Wchnschr.*, 1932, 11:2097-2103.
10. Krause, F.: Hyperinsulinismus mit hypoglykämischen Symptomenkomplex. *Klin. Wchnschr.*, 1930, 23:46-2349.
11. Frank, Heinz: "Letale Hypoglykämie bei Pankreasadenom." *Deutsches Arch. f. Klin. Med.*, 171:175-184, 1931.
12. Wilder, R. M.; Allen, F. N., and others: Carcinoma of islands of pancreas: hyperinsulinism and hypoglycemia. *J. A. M. A.*, 89:344-355, 1927.
13. Theohari, A., and Angelesco, H.: Spontaneous hypoglycemia; therapy. *Rec. éunt. med.*, 21:325-334, March, 1932.
14. Lami, G.: Functional hyperinsulinism. *Clin. Med. ital.*, 61:264-278, May-June, 1930.
15. Peco, F.: Disturbances of carbohydrate metabolism; hypoglycemia. *Sigro. med.*, 89:542-547, May 21, 1932.
16. Marano: Reference misplaced but translated from an Italian journal.
17. Federoff, P. C.: Clinical course of hyperinsulinemia. *Vrap. gaz.*, 35:585-592, April 30, 1931.
18. Harris, Seale: *Am. Jour. of Diges. Dis. and Nutri.*, Vol. 1, No. 8, pp. 562-569, October, 1931.
19. Wilder, Russell M.: Hyperinsulinism. *Internat. Clinics*, 43: Vol. 2, pp. 1-18, 1933.
20. Winans, H. M.: Chronic hypoglycemia. *So. M. J.*, 23:402-405, May, 1930.
21. Harris, Seale: Hyperinsulinism and Dysinsulinism. *J. A. M. A.*, 83:728-733, Sept. 6, 1924.
22. John, H. J.: Lack of uniformity in the insulin reaction. *Am. J. Med. Sci.*, 172:196, 1926.
23. Womack, N. A.; Gnapf, W. B., Jr., and Graham, E. A.: Adenoma of the islands of Langerhans with hypoglycemia: successful operative removal. *J. A. M. A.*, 97:851-856, Sept. 23, 1931.
24. Quisley, J. P.; Johnson, V., and Solomon, E. L.: Action of insulin on the motility of the gastro-intestinal tract. I. Action on the stomach of normal fasting man. *Am. J. Physiol.*, 90:89-94, Sept., 1929.
25. Heinz, T. E., and Palmer, W. L.: A study of the effect of insulin on gastric motility. *Proc. Soc. Exper. Biol. and Med.*, 27:1047-1049, June, 1930.
26. LeBarre, Jean, and Destree, Pierre: L'influence des variations glycémiques sur la motilité gastrique. *Compt. rend. Soc. de Biol.*, 103:532-534, Jan. 25, 1930.

#### DISCUSSION:

DR. JULIUS FRIEDENWALD (Baltimore, Md.): Great credit is due Seale Harris who, as early as 1923, recognized hyperinsulinism as a distinct disease entity and pointed out that symptoms identical with those noted in diabetes from overdoses of insulin occurred in non-diabetics as well. Since then, numerous important observations concerning this condition have been recorded in which to a large measure the work of Seale Harris has played an important rôle.

He has pointed out 3 types of hyperinsulin, the mild, moderately severe and severe forms, ranging from mild symptoms of a nervous character often classed as forms of anxiety neuroses to extreme prostration—with short periods of unconsciousness, lapses of memory, irritability and finally to prolonged and recurrent attacks of unconsciousness and even convulsive seizures.

Among these symptoms those relating to the digestive tract play an important part. It is not uncommon to observe for example hyperinsulinism mimicking the symptoms of so-called ulcer, chronic gastritis, cholecystitis, nervous indigestion and even mucous colitis.

In the ulcer type of hyperinsulinism hunger pains followed by the relief from food is frequent. In some instances a definite epigastric painful area may even be present. The symptoms are not, however, always entirely typical of ulcer. Physical weakness and nervous symptoms are usually prominent and the Roentgen-ray signs of ulcer are absent as is likewise the presence of occult blood in the stools. However, actual duodenal ulceration may occur in association with hyperinsulinism. Harris has reported such instances and we have had a similar experience.

In those instances in which hyperinsulinism simulates chronic cholecystitis the attacks of weakness and sweating occur on an empty stomach and are relieved by food; and in addition are associated with recurrent abdominal pain in the gall bladder region with tenderness in this area. As a rule but little or no direct evidence of cholecystitis can be

discovered; but occasionally a definite associated lesion in the form of gall stones may be demonstrated.

In a single instance of chronic alcoholic gastritis a high degree of hyperinsulinism was noted on arising in the morning previous to and subsequent to such symptoms as nausea, excessive vomiting in association with weakness, faintness, tremor and nervousness, which was entirely overcome as soon as food could be retained.

Certain types of so-called gastrointestinal neuroses may likewise be due to an underlying hitherto undetected hyperinsulinism. The symptoms of excessive weakness, bulimia, tachycardia together with abdominal distention, fullness and aerophagia, so common in these cases are not infrequently associated with spastic colitis and other functional digestive upsets. The fasting blood sugar may be extremely low and proper dietetic regulation is usually followed by entire relief.

In some instances of hyperinsulinism definite chronic pancreatitis may be demonstrated by means of a study of the pancreatic secretion obtained through the duodenal tube, while in others pancreatic tumors have been shown to occur. It may be of interest to note that in a series of experiments on dogs in which sugar metabolism and blood studies were made following vagotomy, Feldman, Samuel Morrison and I observed that symptoms of hyperinsulinism, especially in the form of nausea and vomiting were more apt to manifest themselves following the administration of insulin than in non-vagotomized animals.

In conclusion, the impression gained from the observations of Seale Harris and others is that in all instances in which gastrointestinal symptoms are prominent when associated with those commonly manifested in hyperinsulinism even though these be quite mild, the diagnosis must be promptly established by means of blood sugar investigations.

DR. FRANK SMITHIES (Chicago, Ill.): Naturally, I came here to learn. Inasmuch as Seale Harris was going to deliver this address, it seemed to me an opportune time to learn of this syndrome from the fountainhead.

There are other accidental factors which come in this type of ailment, but it appears to me that frequently when one partakes of an abnormal or unbalanced diet, not only do we have the steaming up of the secretion of the pancreas with the production of extraordinary secretion, but in association with that we have variations in the production of hydrochloric acid and pepsin. We have, in other words, stimulated a link in the digestive system before we reach the pancreas. When we have normal gastric secretion, then we can expect normal pancreatic secretion and normal biliary tract secretion.

Out of curiosity I went through a number of patients who had duodenal ulcer and other ailments. We found that in the duodenal ulcer patients, 9½% of them had blood sugars lower than 100, but none lower than 70; gastric ulcer, 7%; gall bladder ailments 11½%; so-called nervous indigestion, 4½%; epileptic cases in the young individuals, 38 cases (of course, I don't see many epileptics), 5+ had blood sugars lower than 100, and not any lower than 70. Of feeble people, especially older people who had lost the habit of eating either through finickiness or failure of appetite from inertia (if we can use that term), in 17% there was a blood sugar lower than 100, but not lower than 70.

Now, putting the horse into the shafts, (I have given you the cart here before the horse)—it may be interesting to note that while I have seen to a certain degree manifestations of hypoglycemia similar to those described by Dr. Harris, and to those described by the Mayo Clinic, yet in individuals in whom I suspected that I had typical instances and watched the blood sugars for a week or ten days, I was vastly disappointed to find I didn't have lowered blood sugar readings. These patients were secre-



ting normally, provided they ate with any degree of rationality.

I am not here to deny the syndrome that may be due to hypoglycemia. Far be it; yet, on the other hand, I believe that unless we are very careful, we are going to pay too much attention to blood sugars. In estimating them there are possibilities for many sorts of error. We are going to pay too much attention to that observation alone and not enough to noting other disturbances which the patient manifests: disturbances due to disease, or disturbance in function which may be traced to something more definite than hypersecretion of the pancreatic gland.

DR. MAX EINHORN (New York, N. Y.): If I am allowed to say a few words, some years ago I described a condition in which the pancreas secreted too much, gave too much juice. I called it *hyperchylia pancreatica*.

The way I found it was that people who had intense diarrhea, were run down a great deal, and then tried to ascertain how much secretion would run up from the duodenum—if you had the tube in, there would be pancreatic juice in several minutes, and I measured it with regard to the normal and found in those cases I had about three or four times as much; I described such patients as having *hyperchylia pancreatica*.

I am sorry to say that I did not take the blood sugar, but in these cases I surmised that there would be found also probably too little, a small percentage of blood sugar would be present.

I think we are all very grateful to Dr. Harris for bringing up that topic and I would only add that in my cases atropine helped a great deal; I had cases where the pancreas was at fault due to too much action, and by giving atropine and treating in that way, we could bring on quite some improvement.

In this connection I would also say that Boldyreff, the associate of Pavlov, was of the opinion that insulin was a secondary product which is formed in the blood after the pancreatic juice is secreted, so here would be a connection between hyperinsulinism and *hyperchylia pancreatica*.

DR. SEALE HARRIS (Birmingham, Ala., closing the discussion): I predict that within the next year most of those present will have had one case, or a number of cases, of hyperinsulinism. In other words, when gastro-enterologists become "hyperinsulinism conscious," they find the

cases; because such patients usually connect their symptoms with their stomachs.

Three years ago I delivered an address on hyperinsulinism at Shreveport. Since then, Dr. Powell, a Louisiana doctor, has reported twenty-five cases. Incidentally, this general practitioner was the first to suggest that cerebral malnutrition is the cause of the symptoms in hypoglycemia. He noted in an editorial of the Journal of the A. M. A., a statement by Ziegler to the effect that the brain derives its nourishment entirely from glucose circulating in the blood. Heimwich, of Yale, says it is lactic acid that is metabolized in the brain, a product of glucose; but at any rate, Powell observed that when one of his patient's blood sugar went down to 60 or 50, the child could not learn anything, was irritable and below par mentally; whereas, when the child's blood sugar was over 70, she learned her lessons easily and was happy and contented.

Careful questioning of patients who come to gastro-enterologists with suspected gastric ulcer or duodenal ulcer, will in many cases bring out that in addition to the pain three or four hours after eating, they are weak and nervous, and perspire freely until they are relieved by eating. If at the time a blood specimen is obtained for a routine Wassermann enough blood is drawn to make a blood sugar test, low fasting blood sugars will be found more frequently than positive Wassermans. All cases of hyperinsulinism, however, do not have low fasting blood sugars, but where there are symptoms, if the dextrose tolerance test is carried out for six full hours, hypoglycemia, often reproducing the symptoms, will occur in four, five or six hours.

Abdominal pain between meals and during attacks of unconsciousness has been pronounced in several reported cases, so that a number of hyperinsulinism patients have been subjected to needless operations in which erroneous diagnoses of appendicitis, duodenal ulcer, or cholecystitis have been made. Hyperinsulinism has frequently occurred in patients who have proved abdominal lesions, including duodenal ulcer, cholecystitis, pancreatitis, and tumors of the islands Langerhans. Dietary management usually controls or cures hyperinsulinism in intelligent cooperative patients; but resection of the pancreas and removal of insulomas have produced clinical cures in hyperinsulin patients who were not relieved by dietary management.

## ABSTRACTS

FRANK H. LAHEY, M.D., AND G. E. HAGGART, M.D.

*Hyperparathyroidism. S., G., and O., Vol. 60, No. 6, June, 1935.*

In this paper the authors present an excellent review of the subject of hyperparathyroidism together with a report of five new proven cases with the significant findings which led to the diagnosis. The operative exposure for removal of a parathyroid adenoma is illustrated, with particular emphasis upon the possible atypical location of parathyroid bodies—and so these tumors.

The diagnosis of the clinical entity, hyperparathyroidism, depends primarily upon (1) An analysis of the chemical findings and (2) A careful survey of the roentgenograms, including not only those of the bones of the skeleton (especially plates of the skull, spine, pelvis and femora) but also X-rays of the kidneys. The latter plates are taken to demonstrate the presence or absence of calculi. In very early cases of hyperparathyroidism, or in the presence of severe renal damage, study of the chemistry and X-ray findings may be misleading, and the diagnosis not arrived at.

The authors classify cases of hyperparathyroidism clinically into three groups, i.e.:

(1) Classical—The osteitis fibrosa cystica of von Recklinghausen's. Skeletal X-ray of these patients are quite characteristic showing not only the diffuse granular osteoporosis, but also the presence of multiple cysts.

(2) Hyperparathyroidism with osteoporosis—these cases are an early stage of group one and rarely show cyst formation. The decalcification of the bone is not as advanced as in group one, but there is present the characteristic osteoporosis.

(3) Cases in which renal pathology, due to the precipitation of calcium phosphate, is the significant finding. In these cases X-rays of the skeleton are often negative.

The majority of the reported cases have occurred in females between 30 and 50 years of age. From an analysis of 115 proven cases, Gutman, Swenson and Parsons state that pain in the back or extremities was the major initial symptom in 72 per cent, while 22 per cent primarily complained of muscle weakness. The possibility of hyperparathyroidism must always be considered in patients who complain of relatively diffuse "neuritic" or "arthritic" pains, made worse by motion. This is particularly true if the symptoms exhibit localized or general bone tenderness, and if there is a history of pathological fracture.

Charles T. Sturgeon, Los Angeles.

## SECTION V—*Therapeutics*

### The Treatment of Amoebiasis With Iodoxyquinolin Sulphonic Acid \*

By

F. W. O'CONNOR, M.R.C.S.

and

C. R. HULSE

NEW YORK CITY, NEW YORK

IN 1930 the writers reported the results of treatment with iodoxyquinolin sulphonic acid (anayodin) in fifty-one cases of *Entamoeba histolytica* infection. Since our experience has, on the whole been satisfactory, this form of treatment has been continued in 102 additional cases with the results to be described. These may well be considered in four groups.<sup>†</sup>

In the *first group* are thirty cases of acute amoebic dysentery in the stools of each of which actively motile trophozoites, some containing red blood cells, were found. The high percentage of acute cases is due to the advent of the Chicago outbreak in 1933-34 when twenty of these patients definitely attributed the infection to their sojourn in two hotels in that city. These cases were particularly severe and some of them were fulminating in type.

In the *second group* are thirty-eight missionaries either suffering from subacute dysentery, diarrhea, or general ill health with or without histories of dysentery, in whose stools cysts or pre-cystic forms and occasionally, trophozoites of *E. histolytica* were found. The foreign mission fields from which these patients had returned were: Africa 11, Brazil 8, China 6, East India 3, Mexico 1, Philippines 3, Persia 2, Peru 1 and Chosen 3 respectively. In this group two families showed a high incidence of infection with the parasite. In one family from West Africa *E. histolytica* cysts were found in the stools of both parents and four children, while in another family from Brazil the mother, father and two children were found to be infected.

In the *third group* are nineteen *E. histolytica* carriers amongst locally born American citizens who had not traveled outside the northern United States. They were examined for various indispositions and the parasites were found during routine examinations. Some of these patients gave histories of diarrhea with or without the passage of blood and mucus.

In the *last group* are fifteen foreign born residents or United States citizens who had traveled in various,

(including tropical and subtropical), countries. Most of these gave a history of diarrhea or dysentery.

In the whole series *liver abscess* was diagnosed six times. The condition occurred in two of the acute cases originating in Chicago and in two of the local cyst carriers who had never been to Chicago or traveled outside the United States. Neither of these patients gave a history of diarrhea or dysentery. In the sixth case, the patient, a citizen of this country, had lived for some years in the West Indies. He had not suffered from dysentery. *E. histolytica* cysts were found in the stools as confirmation of the diagnosis of hepatic abscess.

#### TREATMENT

All the cases suffering from acute intestinal amoebiasis and all the carriers were treated with anayodin, four pills three times daily with meals for eight days. For those persons in whom the diarrhea was increased by treatment the dosage was reduced to three or two pills, three times a day, but in all cases treatment was continued until the full course of ninety-six pills had been taken.

One patient affected with cardiac disease and very acute dysentery failed to react to treatment. Despite several courses of anayodin and later, courses of carbarsone, vioform, ipecachuana by duodenal tube, emetine alone, or in combination with the other treatments, there was throughout no diminution in the numbers of free phagocytic amoebae and the patient continued to pass blood and mucus. This patient, despite her condition with extensive ulceration of the rectum as seen by proctoscope, complained of neither pain nor local tenderness. Eventually, she developed auricular fibrillations and died suddenly of heart failure. There was one other case of hyposensitiveness amongst the acute cases. This case recovered. He had noticed blood and mucus for several weeks before the condition was discovered but stated that he had not experienced pain, tenesmus or discomfort. Both of these patients were stout types.

With the exception of the fatal case described all the other cases (95) not complicated with liver abscess made an uninterrupted recovery following treatment with iodoxyquinolin sulphonic acid (anayodin) treatment. In their stools, re-examined at intervals during

\*From the Department of Medicine, Presbyterian Hospital, Columbia University, New York City.

Read before the Pan American Medical Association at sea, 7-22-35.

†Note: Complete protocols of these cases are at the Presbyterian Hospital or in the possession of the writers but for purposes of brevity are not given here.

Submitted September 12, 1935.

periods varying from a minimum of six months to several years, *E. histolytica* in any form has not been discovered.

One patient with advanced diverticulosis (demonstrated by roentgenogram) required three courses of treatment with the drug before amoebae disappeared permanently from the stools. In the other cases only one course of treatment was found to be necessary.

The treatment of the liver abscess cases required separate consideration. In one case the patient developed lobar pneumonia during treatment with anayodin for acute dysentery. Anti-amoebic treatment was stopped owing to the gravity of the latter condition. Subsequently convalescence was interrupted by rapid enlargement of the liver, local tenderness and all the other classical clinical, roentgenological and hematological signs of hepatic abscess. Cysts of *E. histolytica* were then found in the stool. The patient was treated with a full course of emetine hydrochloride,  $\frac{1}{2}$  grain twice a day hypodermically for twelve days together with the usual course of anayodin. Signs and symptoms of liver involvement disappeared and the patient made an uninterrupted recovery.

One patient had been treated with anayodin but subsequently died of pre-existing aortic disease. At autopsy a large liver abscess was found in the right lobe of the liver. In the walls of this abscess *E. histolytica* were found in microscopical sections. No amoebae were found in the healing intestinal ulcers.

In two cases operation was performed to evacuate from the liver pus in which amoebae were found and these patients were treated with combined courses of anayodin orally and emetine hydrochloride hypodermically.

In two other cases after hepatic abscess of amoebic origin was definitely diagnosed treatment with emetine and anayodin as already described, was followed by disappearance of symptoms and subsequent recovery.

### SUMMARY

From six years experience, during which one hundred and fifty-two cases of *E. histolytica* infection have been treated, there seems reason to believe that in intestinal amoebiasis iodoxyquinolin sulphonic acid (anayodin) is a very useful drug. It is now shown to be as effective in stopping severe symptoms rapidly and curing acute cases as it is in curing carrier cases. It will not cure all cases any more than any other drug known for the treatment of this infection.

During or following its administration no toxic symptoms have been observed by the writers or their colleagues. In some cases the full dosage increases the diarrhea and causes a scalding sensation during defecation. These symptoms may be eliminated by reducing the dosage without discontinuing the treatment.

Anayodin alone is useless in the treatment of hepatic amoebiasis. When liver abscess is diagnosed present experience suggests that treatment with emetine hydrochloride hypodermically promptly carried out with the necessary precautions may stop further abscess extension. In such cases the administration of a full course of anayodin at the same time seems warranted to prevent later reinfection of the liver from the intestine.

### REFERENCE

- O'Connor, F. W., and Hulse, C. R. (1930): The Treatment of Amoebiasis with Anayodin. *Nineteenth Annual Report of the United Fruit Co. Medical Dept.*, 1930.

## ABSTRACTS

CALLENDER, C. L.; RUSH, G., AND NEMIR, A.

*Mechanism, Symptoms, and Treatment of Hernia Into the Descending Mesocolon (Left Duodenal Hernia). A Plea for a Change in Nomenclature.* S., G., and O., Vol. 60, No. 6, pp. 1052-1071, June, 1935.

The authors report a case of left duodenal hernia giving an explanation of its occurrence in embryology, and some reasons for changing the nomenclature of this lesion. The hernia reported contained the entire small bowel in a sac formed by the descending mesocolon; it was discovered accidentally at necropsy. The anterior wall of the sac contained the inferior mesenteric vein.

The embryology of the intestinal tract is reviewed and it is pointed out that the fossae about the duodenum may be shallow with strong walls or they may be very deep with relatively weak walls. During fetal life, before the descending and transverse mesocolon have undergone agglutination, the fossae about the duodenum are deep; their walls are thin and entrance into their depths is readily accomplished. The authors feel that a portion of the small bowel falls behind a portion of descending mesocolon and becomes incarcerated there. As the bowel increases in length, the body of the cavity enlarges while the continued rotation of the bowel and its agglutination with the pos-

terior parietal peritoneum fixes the opening into the sac. The position of the vascular channels strengthens the free margin of the sac.

The authors propose naming the herniae according to the structures which form the anterior wall of the sac, such as "hernia into the descending mesocolon," "hernia into the ascending mesocolon."

Such herniae frequently do not cause any symptoms; they are usually discovered during laparotomy or necropsy. They should be suspected in a patient who has had repeated attacks of intestinal obstruction. If a large ovoid or globular, doughy or soft mass is visible or palpable filling the upper left part of the abdomen this type of hernia should be suspected.

The treatment of hernia into the descending mesocolon may be very difficult or very easy. If the hernial sac may be emptied manually that should be done. The neck of the sac may be enlarged upward or downward as far as the dissection may be made without injuring any of the vascular trunks around the neck of the sac. As a last resort, the anterior wall of the sac may be incised in an avascular area and the sac explored. The rent in the sac should be repaired after the obstruction has been released.

N. M. Percy, Chicago.

## SECTION VII—*Surgery of the Lower Colon and Rectum*

### The Specificity of the Frei Test in Lymphopathia Venerea\*

By

HARRY E. BACON, B.S., M.D., F.A.C.S.  
PHILADELPHIA, PENNSYLVANIA

THIS fascinating disease entity — lymphopathia venerea or lymphogranuloma inguinale—is of particular interest to us as proctologists by virtue of its interrelationship with various anorectal syndromes, especially stricture of the rectum and esthiomene which now are to be considered the most important sequelae of L.V. The subject is such a massive one and the literature so voluminous that in this brief space we will confine our remarks to but one phase of the disease, namely the specificity of the Frei reaction.

Many are prone to question the existence of such an affection as lymphopathia venerea as well as the value and reliability of the Frei test (42). We earnestly entreat our colleagues, however, to judge unbiasedly by the writings and experimentations of pioneer workers in this field of research. In a recent article by the Author (10) the ubiquity of this disease was cited in reports by 158 investigators representing twenty-one different countries of the world. Each of this number had confirmed the Frei test as a diagnostic aid. Surely the authenticity of the reports offered by such scientists as Levaditi, Hellerstrom, Wassen and Bensaude is not to be derogated. Is not the fact that in patients with a positive Frei test, experimental transmission of the unknown virus by inoculation with pus from an unopened bulbo (106) and tissue from a rectal stricture (66, 86) through guinea pigs into monkeys, with the production of a typical meningoencephalitis which histologically corresponds to the lesion in the human, to be considered a conclusive proof? Further evidence may be cited in that the lesion so produced in the monkey, when prepared according to Frei's technique, gave a positive reaction when injected intradermally into the forearm of patients known to be affected with this disease. Leadrich states that "The experiments prove in a striking manner the specific value of Frei's intradermo-reaction and at the same time the incontestable etiologic role of Nicolas-Favre's disease in stenosing proctitis." Fischer (37) remarks "the intradermal test of Frei shows rather conclusively that stricture of the rectum and chronic granulomatous ulceration of the anus and vulva are due to the specific virus of L.V." Cole (20), who has observed a large number of these cases, mentions that the Frei test has

been of particular value in the diagnosis of the so called "anorectal syphiloma of Fournier." Bensaude (14), in describing the value of the Frei test remarks "The obscure and much discussed etiology of rectal stricture seems to be finally explained by the knowledge of lymphogranulomatosis inguinalis and which must now be added to the list of venereal diseases." Martin (75), who was the first to call our attention in Philadelphia to this interesting disease remarks, "the causative factor of stricture of the rectum, esthiomene and certain other anorectal infections which particularly appear to be an affection peculiar to the Negro race, has been we feel finally solved by the work of Nicolas, Durand, Favre and Frei." In an excellent article on the subject, Bloom (17) declares, "the problem of inflammatory stricture is inseparable from esthiomene." We believe, as others, that in a large percentage of cases this affection is part of L.V. A series recently tabulated by Hellerstrom (54), with their Frei reactions, is as follows:

#### ESTHIOMENE

| Authors                     | Number of Cases | Frei Positive |
|-----------------------------|-----------------|---------------|
| Frei and Koppel             | 12              | 12            |
| Kleeborg                    | 14              | 14            |
| Bensaude and Lambling       | 21              | 19            |
| Barthels and Biberstein     | 7               | 7             |
| Jersild                     | 12              | 12 (11)       |
| Gregorio                    | 27              | 27            |
| Gay Prieto                  | 21              | 19            |
| Ravant                      | 19              | 19            |
| Nicolau                     | 14              | 14            |
| Lohe                        | 10              | 10            |
| Hurwitz                     | 8 - 12          | 8 - 12        |
| DeWolf                      | 7               | 7             |
| Cedercreutz                 | 5               | 5             |
| Peterson                    | 6               | 6             |
| Kitchevatz                  | 3               | 3             |
| Fischer and Schmidt-LaBaume | 5               | 5             |
| A. W. Meyer                 | 4               | 4             |
| Lutz                        | 4               | 4             |
| H. Strauss                  | 3               | 2             |
| Langer and Engel            | 2               | 2             |
| Strombeck                   | 1               | 1             |
| Peyri                       | 1               | 1             |

Total

206 - 210 201 - 205

\*From the Departments of Proctology, Graduate Hospital, University of Pennsylvania, Temple University and St. Luke's Hospitals.

\*Read at the thirty-sixth annual meeting of the American Proctologic Society, Atlantic City, June 10th and 11th, 1935.

Submitted August 5, 1935.

It is interesting to note that Ravaut, Levaditi, and Cachera (86) upon inoculating a guinea pig with ulcerated growths from the anus of a patient with a positive Frei test, observed that a typical lesion of L.V. was produced by transmitting the disease directly to monkeys. Later Meyer and Rosenfeld (79) injected the excised tissue from an esthiomene patient into a guinea pig which subsequently showed a process similar to that of L.V. Loehe (71) and Lutz (73) not only support the interrelationship between esthiomene and L.V. but state that this evidence must be considered conclusive. In four instances we have excised a portion of the esthiomene tissue, which when prepared according to Frei's technic, gave positive intracutaneous reactions in known cases of L.V. Well worth mentioning is the experiment of Nicolas, Favre and Charpy (81) who obtained a positive Frei test in a known L.V. patient with an antigen prepared from the pus of an anorectal fistula. This we have confirmed in a series of six cases.

Many workers in this field have referred to the Frei test as specific for this disease. (99, 87, 9, 52, 55, 33, 92, 85, 97, 18, 84, 82, 65, 64, 63, 62, 59, 47, 45, 61, 56, 38, 40, 35, 23, 7, 8, 11, 15, 13, 68, 31, 32, 43, 108, 104, 36, 76, 4, 5, 70, 103, 2, 19, 110, 112).

A few with their percentage of positive reactions are tabulated as follows:

| Author                               | Bib. | Per-centage | Service | Path-ology Rectal      | Genital |
|--------------------------------------|------|-------------|---------|------------------------|---------|
| Curth, W. (28)                       |      | 100%        | 77      | 50-S.                  | 27      |
| Vander Veer (102)                    |      | 100%        | 46      | 21-S.                  | 26      |
| Hellerstrom, S. (53)                 |      | 100%        | 47      | 0                      | 47      |
| *Hill, M. (58)                       |      | 100%        | 34      | 34-S.                  | 0       |
| Dalton 1934 (29)                     |      | 100%        | 24      | 0                      | 24      |
| Dalton 1935 (30)                     |      | 100%        | 200 ?   | 15                     | 185     |
| Grace, A. (46)                       |      | 100%        | 40      | 20-S.                  | 20      |
| Cole, DeWolf, Van Cleve (20)         |      | 100%        | 52      | 13-S.                  | 37      |
| Lehman, C. F. and Pipkin, J. L. (69) |      | 100%        | 22      | 3-S.                   | 17      |
| Cole, H. 1935 (21)                   |      | 100%        | 100-200 | 2-E.                   | ?       |
| DeWolf, H. 1935 (34)                 |      | 100%        | 3       | 3-S.                   | 0       |
| Van Cleve, J. 1935 (101)             |      | 100%        | 5       | 0                      | 5       |
| Streicher, M. (97)                   |      | 100%        | 19      | 11-S.<br>5-F.          | 3       |
| *Marino, M. (74)                     |      | 100%        | 4       | 4                      | 0       |
| *Hayden, E. P. (50)                  |      | ?           | 20      | ?                      | ?       |
| Grossman, S. (48)                    |      | 100%        | 5       | 4-S.<br>1-A.F.         | 0       |
| *Alley, R. (1)                       |      | 100%        | 20      | 20-S.                  | 0       |
| Burney, L. E. (111)                  |      | 100%        | 10      | -                      | -       |
| Howard, M. and Strauss, M. (60)      |      | 100%        | 16      | 5-S.<br>1-A.F.<br>1-C. | 9       |
| Wien, M. (107)                       |      | 100%        | 16      | ?                      | ?       |
| Bloom, D. (17)                       |      | 100%        | 7       | 7-S.                   | 0       |
| Coutts, W. 1934 (24)                 |      | 100%        | 7       | 2-S.<br>2-A.F.         | ?       |
| Wang, L. and Shen, J. (105)          |      | 100%        | 5       | 2-S.                   | 3       |
| *Templeton and Smith, D. (100)       |      | 100%        | 1       | 1-S.                   | 0       |
| *Martin, C. F. and Bacon, H. E. (78) |      | 96.7%       | 155     | 75-S.<br>56-A.F.       | 24      |
| Sulzberger, M. (98)                  |      | 96.3%       | 27      | 6-S.                   | 21      |
| Strauss, H. (94)                     |      | 96%         | 72      | ?                      | ?       |
| Bensaude, R. (12)                    |      | 90%         | 27      | 24-S.                  | 3 ?     |
| Lee, H. and Staley, R. (67)          |      | 87%         | 16      | 14-S.                  | 2 ?     |
| G. Prieto (83)                       |      | 86%         | ?       | ?                      | ?       |
| Stillman, A. (113)                   |      | 83%         | 6       | 6-S.                   | 0       |
| Corcoran, M. (22)                    |      | 75%         | 4       | 3-?                    | ?       |
| Coutts, W. 1933 (27)                 |      | 68.7%       | 32      | ?                      | ?       |
| *Hayes, H. and Burr, H. (51)         |      | 60.4%       | 106     | 106-S.                 | 0       |

S.—Stricture  
A.F.—Abscess and Fistula  
\*—Members of A.P.S.

C.—Condylomata  
E.—Esthiomene

In order to substantiate the intracutaneous test of Frei, Coutts and Bianchi (26) studied the Bordet-Gengou complement reaction in relation to different

syndromes of L.V. by using an antigen prepared from the lymph nodes as a receptor. After months of research these authors (25) report that this complement fixation is specific for L.V. and supports Frei's intra-dermal test. Another experiment worthy of mention is that by Strauss (93) who found that where the Frei test is strong enough to cause vesicle formation, the content of this vesicle is capable of producing reaction similar to that of the Frei in patients with L.V. In our series of 155 cases, 150 gave a positive Frei test, or 96.7%. Thirty-six different antigens were used, 25 from our cases and the others sent to us by Van Cleve, Hill, Hayden, Strauss, McKenney, Jelks and Reimann in the U. S. and Almanza in Bogota, Hellerstrom in Stockholm, Levaditi in Paris, McDonagh and Stannue in London, and Coutts in Chile. Each test was verified always using a second antigen, usually a third and frequently a fourth. Through the courtesy of Drs. Coca and Roberts, we have utilized the saline suspension of mouse brain prepared by the Lederle Laboratories and find that it compares favorably with our own antigen and those received from others. In order to evaluate the test properly a control antigen obtained from the normal gland of patients not affected with L.V. was used as suggested by Martin (77). In some instances a sterile suspension of leukocytes was injected, while in other cases a control of 0.25 per cent phenol in normal saline solution, as mentioned by Wang (105), was utilized. All controls were negative.

#### TOTAL NUMBER OF CASES SHOWING POSITIVE FREI TEST—150

##### SEX

Females ..... 85  
Males ..... 65

##### RACE

Colored ..... 118  
White ..... 31  
Chinese ..... 1

##### FEMALES

Colored ..... 71  
White ..... 14

##### MALES

Colored ..... 47  
White ..... 17  
Chinese ..... 1

##### AGE

| FEMALES     | AGE | MALES       |    |
|-------------|-----|-------------|----|
| 17-29 ..... | 38  | 14-29 ..... | 27 |
| 30-39 ..... | 27  | 30-39 ..... | 16 |
| 40-49 ..... | 15  | 40-49 ..... | 12 |
| 50-61 ..... | 5   | 50-59 ..... | 7  |
|             |     | 60-73 ..... | 3  |
| Total       | 85  |             |    |

#### PATHOLOGY:

##### FEMALE

Stricture (alone) ..... 59  
Stricture and esthiomene... 4  
Esthiomene (alone) ..... 2  
Abscess and Fistulae..... 12  
(multiple)  
Post-anal infection ..... 4  
Ulcerative procto-colitis... 1  
Anal stenosis ..... 3

Total ..... 85

## PATHOLOGY:

| MALE                      |    |
|---------------------------|----|
| Anorectal stricture ..... | 7  |
| Abscess and Fistula ..... | 22 |
| Anal stenosis .....       | 8  |
| Post-anal infection ..... | 4  |
| Inguinal adenitis .....   | 24 |
| Unilateral .....          | 13 |
| Bilateral .....           | 11 |
| Total                     | 65 |

In an attempt to rule out various diseases such as syphilis, gonorrhea, tuberculosis, and *ulcus molle*, which may cause or at least have been considered the etiologic factors in L.V., certain laboratory tests were performed. Of the 150 cases herein reported, the blood Wassermann and Kahn, and in some instances the Kolmer and Eagle, were taken in 97 instances. At the suggestion of Dr. Edwin Gault a small series was given provocative doses of neoarsphenamine. Seventeen patients showing a negative Wassermann reaction were injected with 3 mgr. after which another test was taken. In each case the report was negative.

| REACTION       | Number      |
|----------------|-------------|
| Negative ..... | 71          |
| Positive       |             |
| / 4 .....      | 22          |
| / 3 .....      | 3           |
| / 2 .....      | 0           |
| / 1 .....      | 1           |
|                | 26 or 26.8% |
| Total          | 97          |

We wish to mention that in our series of 155 cases, 150 of which showed a positive Frei test, three of the five remaining showed a positive Wassermann reaction. During the institution of antiluetic treatment and even after the completion of the course, we failed repeatedly to obtain a positive Frei test. Apparently there exists a reciprocal immunologic reaction between syphilis and L.V. which thus far has not been explained, for it has been observed (39, 16) that in the presence of a recent or an active syphilitic process the Frei test may be rendered temporarily negative.

Smears for the gonococcus were taken in a limited number of cases. Two smears were taken and each stained by the Gram technic. The results were noted as follows:

| Rectal Smears for G. C.  |            |
|--------------------------|------------|
| Negative .....           | 28         |
| Positive .....           | 6 or 17.6% |
| Total                    | 34         |
| Vaginal Smears for G. C. |            |
| Negative .....           | 41         |
| Positive .....           | 13 or 24%  |
| Total                    | 54         |

Reenstierna Test for chancreoid infection (87, 88, 89). Through the courtesy of Almanza of Bogota and Reenstierna of Stockholm, we obtained a supply of Dmlecos vaccine (suspension of *B. culey* and streptococcus) which is considered specific for chancreoids (3, 57, 109) termed on the Continent *ulcus molle*. Forty-one cases showing a positive Frei test were injected intradermally with 1-10 c.c. of the Dmlecos vaccine. Thirty-eight gave a negative reaction. Of the three showing a positive Reenstierna test, two of this number presented clinical evidence of chancreoid infection.

| NUMBER         |    |
|----------------|----|
| Negative ..... | 38 |
| Positive ..... | 3  |
| Total          | 41 |

In one instance we attempted to transmit the Ducrey organisms to the forearm of the patient after scarification but without success.

*Tuberculosis.* To determine the presence or absence of tuberculosis is a most perplexing problem especially when applied to the use of tuberculin. Either it is inert in a large percentage of instances or there is considerable chance of falsely interpreting many reactions as positive. The new standard tuberculin termed "Purified Protein Derivative" (P.P.D.), prepared by Seibert (90, 91) and adopted by the National Tuberculosis Association, is considered of greater value than O.T. (49, 72, 80) in that it is free of salts and non-specific proteins and that its potency is reproducible (6). With the assistance of Dr. Gault, Pathologist to the Temple University, School of Medicine, forty-five patients in our series were tested intradermally with P.P.D., using the first dilution (0.00002 mg.). Their reactions were read and measured in 48 hours. The second dilution (0.005 mg.) was injected in cases that were negative to the first. The results were as follows:

| Reaction                                                                           | Number |
|------------------------------------------------------------------------------------|--------|
| Negative                                                                           | 33     |
| Positive 1 reaction shows area of swelling measuring 5 to 10 mm. in diameter ..... | 1      |
| 2 reaction shows area of swelling measuring 10 to 22 mm. in diameter .....         | 5      |
| 3 reaction shows area of swelling exceeding 20 mm. in diameter ..                  | 3      |
| 4 reaction shows area of swelling and definite necrosis .....                      | 3      |
| Total                                                                              | 45     |

Of the 12 cases showing a positive P.P.D. test, five presented clinical and histologic evidence of tuberculosis: pulmonary 2, fistula 1, nodule 1 and anal skin 1. All, however, showed a positive Frei reaction.

In an effort to determine the percentage of positive Frei tests in various affections other than L.V., we solicited the services of our colleagues in allied clinics. Negative Frei tests were obtained in the following cases:



## FREI TEST CONTROLS

|                                           | Number<br>of Cases |
|-------------------------------------------|--------------------|
| Healthy .....                             | 44                 |
| Colitis, various forms .....              | 21                 |
| Syphilis, — skin .....                    | 4                  |
| Stomach ? .....                           | 1                  |
| Tuberculosis, — intestinal .....          | 3                  |
| pulmonary .....                           | 12                 |
| Gonorrheal urethritis and vaginitis ..... | 9                  |
| Cholecystitis .....                       | 9                  |
| Gastric or duodenal ulcer .....           | 7                  |
| Carcinoma larynx .....                    | 1                  |
| Carcinoma prostate .....                  | 4                  |
| Carcinoma breast .....                    | 1                  |
| Carcinoma stomach .....                   | 5                  |
| Lipoma .....                              | 3                  |
| Actinomycosis .....                       | 1                  |
| Hodgkin's disease .....                   | 1                  |
| Thyroid disease .....                     | 3                  |
| Fractures .....                           | 4                  |
| Pyelitis .....                            | 4                  |
| Influenzal conditions .....               | 14                 |

## RECTAL

|                                     |    |
|-------------------------------------|----|
| Carcinoma, rectum .....             | 9  |
| Benign adenoma .....                | 3  |
| Post-anal ulcer and infection ..... | 12 |
| Hemorrhoids .....                   | 47 |

|                            |    |
|----------------------------|----|
| Abscess and Fistulae ..... | 34 |
| Tuberculous fistulae ..... | 2  |
| Pruritus ani .....         | 6  |

Total 264

In a recent communication to C. F. Martin, Silvers reported a series of 100 control cases from the Atlantic City Hospital in which all gave a negative Frei test.

## CONCLUSION

By repeated testings the Frei test has proven specific and has assisted in the recognition of the heretofore unaccepted therapy of L.V. Over a period of two years we have observed these patients and their Frei reactions in various stages of the disease, and feel that in the presence of clinical evidence one negative test should not be considered as confirmatory that the process is not one of L.V. To a large degree, incorrect readings may be obviated by careful selection of the tissue used, strict adherence to the preparation and preservation of the antigen, its method of administration and time of reading.

We consider the Frei test to be of utmost value in the diagnosis of L.V. judging from our total series of 155 cases bearing a positive percentage of 96.7 that clinically and pathologically presented manifestations of this disease, but we do concur with Guy del Vivo (44) that further and more conclusive evidence should be sought as to its etiology.

## REFERENCES

- Alley, R.: Lymphopathia Venerea. *Trans. Amer. Proc. Soc.*, p. 150, 1934.
- Alley, R.: Lymphopathia Venerea Involving the Rectum. *Kentucky M. J.*, p. 250, Bowling Green, Vol. XXXII, 1931.
- Almkvist, J.: En praktisk behandlingsmetod for ulcus molle. *Allm. Sr. Lakretidn.*, No. 23, 1906.
- Amtmaa, L., and Pilot, L.: Lymphogranuloma inguinale, three cases from Chicago. *Arch. Derm. and Syph.*, Vol. XXVI, p. 868, 1932.
- Amwyl, Davies T.: Lymphogranuloma Inguinale. *Lancet*, Vol. II, p. 289, 1933.
- Aronson, J. D.: Purified Protein Derivative. *Suppl. Amer. Rev. Tuberc.*, p. 727, Vol. XXXVI, No. 2, Dec., 1934.
- Bacon, H. E.: Lymphogranuloma Inguinale, Dise. *Urol. Sect. Penn. State Med.*, Wilkes-Barre, Oct., 1934.
- Bacon, H. E.: Lymphopathia Venerea, Frei test Statistics, Staff Meeting Grad. Hosp., Univ. of Pennsylvania, Feb., 1934.
- Bacon, H. E.: Stricture of the Rectum. *Cyelo. Med.*, Vol. X, p. 1116, F. A. Davis & Co., Philadelphia, 1934.
- Bacon, H. E.: The ubiquity of Lymphogranulomatosis Venerea. Read before the Proc. Soc., Allentown, April 24, 1934.
- Barthels, C., and Biberstein, H.: Zur Ethnologie der entzündlichen Rektumstriktura, Burns. *Beitr. zur Klin., Chir.*, Vol. CLII, p. 161, 1930.
- Bensaude: Quoted by Frei.
- Bensaude, R.: Les retrecissements du rectum. *Bull. Med.*, Vol. XVII, p. 421, 1932.
- Bensaude, R., and Lamblag, A.: The role of Nicolas-Favre's Disease in the Etiology of Inflammatory Stricture of the Rectum. Study in 21 cases with the Aid of Frei's intradermal reaction. *Comp. rend. des seances de la Soc. de Bibliog.*, 108, p. 1950, 1931.
- Bianchi, T. B., and Coutts, W. E.: *Arch. Derm. and Syph.*, Vol. 28, p. 32, July, 1933.
- Biberstein, H. Oschinski: Versuche uber die Empfindlichkeit der menschlichen Haut gegen Tiersern. *Arch. and Dermat. u. Syph.*, 142, 1931.
- Bloom, D.: Strictures of the Rectum due to Lymphogranuloma Inguinale. *S. G. O.*, Vol. LVIII, No. 5, p. 827, May, 1934.
- Buraey, L. E.: Lymphogranuloma Inguinale. *Ven. Dis. Bull.*, 15, p. 233, July, 1934.
- Cedercreutz, A.: Lymphogranulomatosis inguinallis. *Finska Lak. Sallak. Handl.*, Vol. LXX, p. 1036, 1928.
- Cole, H. N.: Lymphogranuloma inguinal, Fourth, Venereal Disease; Its Relation to Stricture of the Rectum. *J. A. M. A.*, Vol. 101, p. 1068, Sept. 30, 1933.
- Cole, H. N.: Personal Communication, May 8, 1935.
- Corachan, M.: Inflammatory Rectal Steatosis. *Arch. de med. Cir. u. espec.*, 35: 429, Madrid, May, 1932.
- Cormin, F. E.: Lymphogranulomatosis Inguinale, A Review of the Literature. *Urol and Cutan. Rev.*, p. 789, Nov., 1931.
- Coutts, W. E.: Genito-Ano-Rectal Lymphogranulomatosis of the Male. *Ann. Surg.*, Vol. XCIX, No. 1, p. 188, Jan., 1934.
- Coutts, W. E., and Ponce, T.: The Complement Fixation in the Diagnosis of Lymphogranulomatosis Venerea. *Jour. Lab. and Clin. Med.*, Vol. XX, No. 6, p. 629, March, 1935.
- Coutts, W. E., and Bianchi, T. B.: Lymphogranulomatosis Venerea and Its Chafical Syndromes. *Urol and Cutan. Rev.*, p. 263, April, 1934.
- Coutts, W. E.; Herrea, J., and Martini and Perroni, F.: Lymphogranulomatosis Venerea. *Amer. Jour. Surg.*, 22, 96, Oct., 1933.
- Curth, W.: Personal Communication, May 8, 1935.
- Dalto, J. E.: Lymphogranulomatosis Inguinalis. *Jour. Indiana State Med.*, p. 158, Vol. 27, No. 14, April, 1934.
- Dalto, J. E.: Personal Communication.
- deGregorio, E.: Elefantiasis y ulceraciones cronicas vulvares. *Act. Derm. Sifil.*, Madrid, 1931.
- deMoabreum, W. A., and Goodpasture, E. W.: Further Studies on the Etiology of Granuloma Inguinale. *Amer. Jour. Trop. Med.*, Vol. XIII, p. 447, 1933.
- DeWolf, H. F., and Vaa Cleve, J. V.: Lymphogranuloma Inguinale. *J. A. M. A.*, No. 13, Vol. 99, p. 1066, Sept. 24, 1932.
- DeWolf, H. F.: Personal Communication, May 13, 1935.
- Dind: Quoted by Hellerstrom.
- Feleheafeld, H.: Etiology of Elephantiasis Vulvae Anorectitis Associated with Rectal Strictures, with Special Reference to Lymphogranulomatosis Inguinale. *Med. Wchenschr.*, 28, 965, July, 1932.
- Fischer, A. W., and Schmidt La Baume: Rectal Strictures and Lymphogranuloma Inguinale. *Deut. med. Wchenschr.*, B. 58, S. 572, April, 1932.
- Fischer, O.: Über eine Hautreaktion bei Klimallischea Buboas. *Klin. Woch.*, p. 6, 1926.
- Frei, W.: Lymphogranulomatosis Inguinalis. *Klin. Woch.*, B. 23, 1927.
- Frei, W.: Lymphogranulomatosis Inguinalis, Die Haut, Geschlechtskrankheiten, Londerdruck nu Band, V. Urban and Schwarzenberg, Berlin, 1931.
- Frei, W.: Der Gagenwrtige stand der Kenntnisse von der Elephantiasis genito anorectnalis. *Deut. Med. Wchenschr.*, Nr. 50, S. 1964, 1932.
- Frei, W.: Eine neue Hartreaktion bei Lymphogranuloma Inguinale. *Klin. Wchenschr.*, B. IV, p. 2148, Nov., 1925.
- Fuchs, H.: Lymphadenitis inguinalis chronica. *Uuklerer, Actiologic, Wiener. Dermat.*, XI, 17, 1927.
- G. del Vivo: *Gior ital di dermat. e sif.*, Vol. 74, p. 735, June, 1933.
- Geisler, H.: The Diagnosis of Lymphogranuloma Inguinale. *Klin. Woch.*, S. 11, 1928.
- Grace, A. W.: Personal Communication, May, 1935.
- Gray, J., and Yieh, J. C.: Lymphogranuloma Inguinale among Chinese. *Chinese Med. Jour.*, Vol. 48, No. 7, p. 607, July, 1934.
- Grossman, S. L.: Lymphogranuloma Inguinale. *Urol. Sect. Penn. State Med. Soc.*, Wilkes-Barre, Oct., 1934.
- Hall, C.: The Value of the Tuberculin Test. *Jour. Kansas Med. Soc.*, Vol. XXXVI, No. 2, Feb., 1935.
- Hayden, E. P.: Personal Communication, May 6, 1935.
- Hayes, H. T., and Burr, H.: Personal Communication, May, 1935.
- Hellerstrom, S.: Contribution à l'étude de la Lymphogranuloma Inguinale, Extract des Annales des Maladies Veneriennes, p. 10, Grande Imprimerie de Troyes, 1929.
- Hellerstrom, S.: Contribution to the Knowledge of Lymphogranuloma Inguinale, p. 117. *Acta. Dermato-Venerologica*, Kungl. Boktryckeriet, Stockholm, 1929.
- Hellerstrom, S.: Epidemiology and Etiology of Lymphogranuloma Inguinale, Lennander Lecture, p. 14, Mnssea et Cie, 1934.
- Hellerstrom, S.: Experience avec l'intradermo-reaction dans la maladie de Nicolas-Favre, Bull. de la Soc. France, Dermat. and Syphil., Mnssea et Cit, Paris, No. 4, April, 1931.
- Hellerstrom, S.: Zur Kenntnis Der Hautallergie Bei Lymphogranuloma Inguinale. *Klin Wchenschr.*, Nr. 13, S. 595, J. 10, Marz, 28, 1931.

57. Herrens, E.: Climate Buboos and Inguinal Lymphogranuloma. *Klin. Wchnschr.*, 7, 2436, 1928.
58. Hill, M. R.: The Frei Antigen Reaction in Benign Rectal Strictures. *Trans. Amer. Proc. Soc.*, p. 163, 1931.
59. Hillman, J. A.; Wilbush, H. F.; and Zimmerman, H. M.: Lymphopathia Venerea and the Frei test. *Brit. Jour. Derm. and Syphil.*, Vol. XLIV, p. 192, 1932.
60. Howard, M. E., and Strauss, M. J.: Lymphogranuloma Inguinale. Report of 16 cases in and around New Haven.
61. Jersild, O.: Intradermal Reaction in Ulcus Molle and Lymphogranuloma Inguinale. *Ann. Derm. et Syph.*, 11, p. 577, 1930.
62. Kitcheratz, M.: A Specific Allergic Reaction in Nicholas-Favre Disease. *Soc. Derm. et Syphil.*, p. 37, 1925.
63. Koch, T.: *Dermat. Ztschr.*, 11, 65, Jan., 1935.
64. Koppel, A.: Lymphogranuloma Inguinale with Rheumatic Symptomatology. *Klin. Wchnschr.*, 52, 1927.
65. Langer, E., and Emde, C.: Zur Frage der Lymphogranuloma Inguinale Recti. *Munch. med. Wchnschr.*, Vol. IX, p. 350, 1932.
66. Landrich, L.; Levaditi, C.; Mamon, H.; and Bauchecase, H.: Inflammatory Stricture of the Rectum, Atypical Aberrant form of Nicholas-Favre's Disease, Inoculation of Apes Positive. *Bull. Men. Soc. Hospit.*, 48, p. 1672, July 4, 1932.
67. Lee, H., and Staley, H. W.: Inflammatory Stricture of the Rectum and Their Relation to Lymphogranuloma Inguinale. *Ann. Surg.*, Vol. C, p. 456, Sept., 1931.
68. Lehman, C. F., and Pipkin, J. L.: Lymphopathia Venerea. *Texas State Med. Jour.*, 23, 192, July, 1933.
69. Lehman, C. F., and Pipkin, J. L.: Personal Communication, May 10, 1935.
70. Lepinay, G.: The Frei Reaction. *Bull. Soc. Franc. Dermat. et Syph.*, 46, 752, May, 1933.
71. Loeb, H., and Rosenfeld, H.: Neue Ergebnisse über die Späel formen des Lymphogranuloma Inguinale. *Med. Klin.*, B. XXXIII, S. 1456, 1932.
72. Long, E. R.; Aranson, J. D.; and Seibert, F. B.: Tuberculin Survey with the Purified Protea Derivative. *Supp. Amer. Rev. Tuberc.*, p. 733, Vol. XXXVI, No. 6, Dec., 1931.
73. Lutz, K.: Eatzuendliche Reklmstricturen durch Lymphogranuloma Inguinale. *Deut. Med. Wchnschr.*, B. LVIII, 1360.
74. Marino, M.: Personal Communication, May 3, 1935.
75. Martin, C. F.: Lymphopathia Venerea, Disc., p. 173. *Trans. Proc. Soc.*, 1934.
76. Martin, C. F.: Stricture of the Rectum. *J. A. M. A.*, Vol. 101, No. 20, p. 1550, Nov. 11, 1933.
77. Martin, C. F.: Lymphopathia, Venerea. *Forum Acc. C.*, Nov., 1937.
78. Martin, C. F., and Bacon, H. E.: Symposium on Lymphopathia Venerea. Staff Meeting Grad. Hosp., Univ. of Pennsylvania, Feb., 1935.
79. Meyer, K., and Rosenfeld, H.: Erfolgreich Uebertragung des Lymphogranuloma Inguinale auf Meerschweinchen. *Klin. Wchnschr.*, Vol. 10, p. 1633, Sept., 1931.
80. Myltinger, W. H.: The Tuberculin Test. *Jour. Indiana State Med.*, Vol. XXVII, No. 12, p. 579, Dec., 1934.
81. Nicholas, J.; Favre, M.; Lebeuf, P., and Charpy, J.: Intra-dermo-reactions positives dans la maladie de Nicholas-Favre avec une ulcération d'une forme anorectale elephantiasique de la maladie. *Bull. Soc. franc. de dermat. et Syph.*, Vol. XXXIX, p. 24, 1932.
82. Nicholas, J.; Favre, M., and Maesin, G.: Retraissement Anorectal Elephantiasique et Lymphogranulomatoses Inguinale. *J. A. M. A., Lyon*, Vol. CCLXXIII, p. 303, 1931.
83. G. Prieto: Quoted by Frei.
84. Prieto, J. G.: The Biological Treatment of Subacute Lymphogranulomatoses with Intravenous Injections of Specific Antigen. *Arch. d. med. Chirug. p. espanol.*, 13 and 85, 1932.
85. Ramel, E.: Beitrage zur Kenntnis der Lymphogranulomatoses Inguinales. *Derm. Zeit.*, Vol. LIII, 1928.
86. Ravaut, P.; Levaditi, C.; Lambing, A., and Canehera, R.: La presence du virus de la maladie de Nicholas-Favre dans les lesions d'une malade atteinte d'anorectite ulcero-vegetante. *Bull. acad. de med.*, Vol. XCVIII, 98, 1932.
87. Reensterna, J.: Recherches Sur Le Bacille de Durey Extrait des arch d l' instit. Pasteur de Tunis, Tome XII, fasc. 3, p. 278, 1932.
88. Reensterna, J.: En Mer An 1 — Arig Ulcus Molle-Infection. *Lakt. Efter Scrumbehandling Lartrack Ur Hygiea*, 1920.
89. Reensterna, J.: Chancre mou experimental chez le singe et le lapin, acta Dermato-Venera, Vol. II, Fasc. Mars., 1931.
90. Seibert, F. B.: Trans. Ann. Meeting. Nat'l Tuberc. Assn., p. 165, 1933.
91. Seibert, F. B.: Isolation and Properties of the Purified Protein Derivative of Tuberculin. *Supp. Amer. Rev. Tuberc.*, p. 713, Vol. XXX, No. 6, Dec., 1934.
92. Seneque, J.: Maladie de Nicolas et Favre et retraissement du Rectum. *Presse Med.*, Vol. II, p. 22, 1932.
93. Strauss, H.: Zur Frage d Atiologie d Venerischen Rektalstretturen. *Dermat. Wchnschr.*, B. 96, p. 235, 1933.
94. Strauss, M. J., and Howard, M. E.: The Frei test for Lymphogranuloma Inguinale. *J. A. M. A.*, Vol. 103, No. 24, p. 1830, Dec. 15, 1934.
95. Stillman, A.: Stricture of the Rectum. *Ann. Surg.*, Vol. 101, No. 5, p. 1284.
96. Stillman, A.: Personal Communication, May 9, 1935.
97. Streicher, M. H.: Rectal Obstruction. *Ill. Med. Jour.*, 64, p. 133, Aug., 1933.
98. Sulzberger, M. B. et al.: Personal Communication.
99. Sulzberger, M. B., and Wise, F.: Lymphopathia Venereum. *J. A. M. A.*, No. 17, Vol. 10, p. 1407, Oct. 22, 1932.
100. Templeton, H. J., and Smith, D.: Lymphogranuloma Inguinale. *California and Western Med.*, 41, p. 42, July, 1934.
101. Van Cleave, J. C.: Personal Communication, May 11, 1935.
102. Vander Veer, J. B.: Personal Communication, April 14, 1935.
103. Vizenrande, E.: La reaction de Frei eu las adenopatias inguinales y en las estre chices reetales. *Gac. Med. de caracas*, 23, 1932.
104. Von Veress, F.: Lymphogranulomatoses Inguinalis. *Derm. Wchnschr.*, 96, 201, Feb., 1933.
105. Wang, L. K., and Shen, J. K.: Lymphogranuloma Inguinale, Report of Five Cases. *Chinese Med. Jour.*, Vol. 48, No. 7, p. 615, July, 1934.
106. Wasson, E.: Transmission of Inguinal Lymphogranulomatoses in Guinea pigs. *Compt. rend. Soc. de Biol.*, Vol. CXVI, p. 121, Paris, 1934.
107. Wien, M. S., and Perlstein, M. O.: Intradermal Treatment of Lymphogranuloma Inguinale Prelim. Report. *Arch. Dermat. and Syphil.*, Vol. XXVIII, p. 42, July, 1933.
108. Wolf, J., and Sulzberger, M. B.: Lymphopathia Venereum and the Frei test. *Brit. Jour. Dermat. and Syphil.*, 44, 192, April, 1932.
109. Yu Tun Pe: The Value of Specific Durey Bacillus Vaccine in the Diagnosis and Treatment of Inguinal Bubo. *Dermat. Wchnschr.*, 99, 1642, Leipzig, Dec. 22, 1934.
110. Zukin, S. J.: Lymphogranuloma Inguinale or Durand Nicholas-Favre Disease. *Arch. Dermat. and Syphil.*, 26, p. 239, Aug., 1932.
111. Burney, L. E.: Personal Communication, May 8, 1935.
112. Martin, C. F., and Bacon, H. E.: Lymphopathia Venerea. Accepted for publication May 3, 1935, International Clinica.
113. Stillman, A.: Stricture of the Rectum. *Ann. Surg.*, Vol. 101, No. 5, p. 1284, May, 1935.

## ABSTRACTS

MORGAN, J. W.

*Pectenosis and Minor Maladies of the Anal Region.*  
S., G. and O., Vol. LIX, No. 5, Nov., 1934, pp. 806-809.

The author wishes to call attention to the importance of the variety of lesions found in the anal canal, and to record some personal observations as to their clinical findings and treatment. A consideration of the anatomy of the part is important. Four landmarks are recognized, namely: (1) the ano cutaneous line which marks the lower end of the intestinal tract; no hair follicles are seen cephalad to this line; (2) the white line of Hilton which lies 1.5 centimeters above the ano cutaneous line. It is from six to nine millimeters in width, and, during life, is blue in color; (3) the pectinate line is represented by the lower margins of the sinuses and columns of Morgagni; (4) the ano rectal line is 1.5 centimeters above the pectinate line; it can be accurately identified only with the aid of the microscope. The pectinate line is the important area as it is here that the blood, lymphatic and nerve supply divide. When the anal orifice is closed, the pecten forms the central part

of the floor of the rectum, and it is reasonable to suppose that it should be the seat of special organs whose function it is to regulate the action of the sphincter muscles. Any disturbance of the equilibrium of the sphincters leads to chronic passive congestion, which in turn leads to round cell infiltration, fibrosis, and the production of a condition termed pectenosis. The fibrous deposit, which varies in breadth and thickness according to its duration, encircles the canal, and was called "the pecten band" by Miles in 1918. Passive congestion may result from many causes; e. g.; hemorrhoids, contusions or lacerations of the canal, irritating liquid stools, etc. The resulting pectenosis persists and becomes more marked, aggravating the primary condition until it is corrected. During the last year and a half the author has operated on 83 patients whose lesions could be explained by the presence of pectenosis and a pecten band. In most cases where the pecten band is well defined simple incision of it affords complete relief. The author warns against the practice of division as it is always dangerous.

N. M. Percy, Chicago.

## SECTION VIII—*Editorial*

*NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastroenterological Association is in no way responsible for editorial expressions.*

### THE DIAGNOSIS OF GASTRITIS

**P**ROFESSOR Katsch reviews the subject of gastritis chiefly from a diagnostic standpoint. Like many of his German contemporaries, he feels that gastritis is a frequent disease, supported by an abundant factual material. Nevertheless, in his opinion, the diagnosis of gastritis remains a delicate matter, a fact of which the general practitioner is aware, and confirmed by the clinician attached to a Clinic where he is occupied intensively with mass pathology.

The Author feels that the unsatisfactory state of the situation concerning gastritis lies in the fact that gastroscopy is a diagnostic procedure reserved for the few specially trained physicians and can hardly be made available to the general practitioner. "Moreover, a clear relation between gastroscopic findings and the clinical picture, even excluding everything but the subjective illness, can be established with any degree of certainty only in cases with clear-out findings. Less pronounced pictures of gastritis are found both in patients with severe symptoms and in those with mild complaints. They may also be discovered by chance in persons who feel quite well. Therefore, a diagnosis made exclusively by gastroscopic examination is not only impracticable in many instances for reasons mentioned, but it is furthermore not to be relied on entirely for the general diagnosis of all cases of gastritis" (1).

**Roentgen Diagnosis:** Katsch regards this procedure as considerably less reliable than gastroscopy. At times the diagnosis of gastritis can be made through visualization of the mucosal relief with a small amount of barium. He feels that granulation of the relief is the most certain roentgen sign. This may be of such extent that folds can no longer be recognized. Such findings are relatively rare however. Changes in the folds may give rise to reliable findings, especially when the fold is not only wide, but shows a confused, unusual type of sinuosity, a rigid course, "against the grain" (Berg), or on longer observation, that rigidity and immobility so familiarly seen in the gastroscopic picture. Another sign of some importance, in the Author's judgment, is the presence of smooth surfaces lying between coarse folds. He discusses at length some of the pitfalls in the diagnosis of gastritis from the appearance of the mucosal folds under certain conditions, as brought out by Forssell, Velde, and others.

**Examination of the cellular sediment in the gastric content:** He discusses the work of Loeper, Kauffmann, Westphal, and Kuekuok. A distinction is made between exudation and the normal desquamation of cells of the gastric mucosa into the lumen of the stomach, the former being of chief diagnostic significance. In the conception of exudation are included the emigra-

tion of leukocytes (leukodiapedesis), and to a less extent the emigration of connective tissue cells (histiodiapedesis). For the present, the most important findings, in the Author's opinion, giving rise to any serious diagnostic consideration, are such cell findings as are notably and crassly abnormal, a leukocytic sediment so marked as to resemble or approach a purulent sediment, a richness in cells so great that one might speak of desquamative catarrh. One must not forget that such findings are also present in cancer.

**The diagnostic role of gastric chemism and functional tests:** It is pointed out that in those cases in which the diagnosis of gastritis has been made on the basis of morphologic findings, it is very seldom that one can predict what the gastric analysis will show as regards the functional capacity of the stomach. The only exceptions are the cases with extensive atrophy of the gastric mucosa. In very high-grade forms of so-called hypertrophic gastritis, and in most cases of erosive gastritis, achylia is also found, at least subacidity in the latter. In the majority of cases functional capacity can be determined only by the functional test. Hence Jaworski and Hayem speak of an anacid, subacid, acid and hyperacid gastritis.

Beyond question a deficiency of gastric juice is the most important functional finding in gastritis. Of course, such finding is present in most cases of carcinoma and in pernicious anemia. The Author also discusses the importance of gastric analysis not only in determining the concentration of the free hydrochloric acid, but the amount of secretion and determination of the total chloride value. The Author describes a simple test for the determination of the latter. The importance of observation, and repetition of the functional tests in cases of gastritis, to determine whether progress or retrogression under treatment is occurring, is emphasized.

**Symptoms:** In patients over forty years of age, who have had infections and alimentary injuries in the past and have been exposed to the action of irritants, gastritis, in the opinion of the Author, is exceedingly common, so that the explanation of even atypical gastric disorders will often come to mind. But even if a diagnosis of gastritis is made, there remains the estimation of the degree of injury to the mucous membrane, the degree of functional disturbance, the nature of the tendency of the chronic inflammatory process, the oscillations of the process between activity and latency, the acute exacerbations and the final defect states; and further, the degree of compensation attained up to the point where digestive processes in the intestine fully make up for the deficiency in gastric digestion. Symptoms, especially intestinal disturbances, appear with gastric decompensation, and the work of Brinck and Gutzeit with reference to gastro-enteritis is mentioned.

The Author discusses briefly some of the variations in the symptom complexes. (1) The patient with a

1. Die Diagnose Gastritis—G. Katsch. Klin. Wehnschr. 14; March 23, 1935, pp. 411-414.

"sensitive" stomach occupies a place close to that of the individual with latent gastritis. The Author has reference to "acidism" (epigastric burning, heartburn, acid eructations) easily occasioned by dietetic error. (2) The pyloric syndrome, closely simulating the symptom complex of duodenal ulcer. The Author, however, points out that in the pronounced chronic cases of this kind, an ulcer of the pyloric region or duodenum is usually found, without exception. (3) The weak stomach which is not equal to more than moderate demands, either qualitative or quantitative, and is not infrequently accompanied by disturbances of taste and appetite, and intestinal disturbances. Cases in which disturbances are primarily intestinal, characterized by diarrhea, constipation, or gaseous distension. (3-a) The hyperchromic anemia of patients with achylia, which react to treatment with iron. (Faber's anemia). (4) Cases of gastric hemorrhage as the result of erosive gastritis in the absence of gross ulcer. This clinical picture has long been emphasized by Konjetzny. (5) Patients with more acutely painful symptoms, the result of acute and subacute stages of gastritis.

The pains are the result, for the most part, of infiltrative inflammations affecting more or less of the gastric wall, and no doubt including the nerve plexuses. This, in the Author's opinion, explains the frequent, almost neuralkic character of the pain. On the one hand, the pain may appear independently of the taking of food and may persist for hours as a constant pain, and on the other hand, the pain may become intensified by the peristaltic movements of the stomach. The Author agrees with Hlenning, that such pains may be aggravated by anything which distends the stomach and by body movements, such as physical exertion, stooping, the putting on of an abdominal belt, etc. In rare cases the pains of gastritis may be so acute and intense, accompanied by board-hard tension of the abdominal wall, so that perforation is suggested. Konjetzny was the first to call particular attention to these cases. There is an associated lymphangitis extending into the subserosa and into the regional lymph glands. The differentiation from perforated ulcer may be impossible without abdominal exploration.

The writer, as others before him, summarized the knowledge gained by gastroscopy, microscopic exami-

nation of freshly resected material, by roentgen examination, and by experimental research. He emphasizes the importance of intensive study in this field, and as soon as possible, the clarification of our knowledge so that the general practitioner may avail himself of its use. A literal translation of the closing paragraph is of interest to workers in this field.

"In order to further our therapeutic ability it will be necessary in the future for us not to rest content with the diagnosis of gastritis but to characterize more accurately the individual states and their transformations. We cannot dispense with a certain many-sidedness of nomenclature. We have on the one hand a nomenclature referring to the gastroscopic pictures (gastritis hypertrophicans, infiltrative, atrophicans, granularis, polyposa, erosiva, haemorrhagica, pseudomembranacea, etc.); one also refers to the gastroscopically determined localization (corpus gastritis, pylorus gastritis). On the other hand, the functional test supplies a nomenclature (gastritis superacida, subacida, anacida, achylia absoluta, achylia perniciososa). Thirdly, there is the nomenclature derived from the clinical pictures and course, (gastritis acuta, subacuta, recurrens, exudans, dolorosa, latens, larvata, chronica, progressiva, etc.) Since there is no simple parallelism between gastroscopic pictures, results of the function test, subjective symptom pictures, the disease has to be considered simultaneously from the morphologic, clinical and functional standpoints and we cannot dispense with a mixture of names obtained according to different points of view and used to supplement one another. It is greatly to be desired that we should have an etiologic nomenclature of gastritis. At present, we can use such a nomenclature in some cases only (gastritis infectiosa, corrosiva, alcoholica, uraemica). In other etiologic designations, such as hepatogenic gastritis (Wichels), and peptic gastritis (Buchner), we sometimes run off into the region of hypothesis. It is particularly for the recognition of what is harmful and what is useful in the various forms of chronic gastritis and for the advance of etiology, prophylaxis and therapy that it is necessary to differentiate and characterize the gastritic stages as accurately as possible and to observe the changes and the course with patience over long periods of time."

George Eusterman, Rochester, Minn.

## SECTION IX—*Book Reviews*

*(This section is open to contributions from any medical reader, whether a member of the Editorial Council or not).*

Traite de Gastroscopie et de Pathologie Endoscopique de L' Estomac, by Francois Moutier, Masson et Cie, Publishers, Paris, 1935.

**T**HIS volume represents an elaborate and most praiseworthy attempt to present the subject of Peroral Gastroscopy in thorough going fashion. The volume is complete, beautifully illustrated and represents the first volume in the French language to explain fully this interesting subject. It is presented along similar lines to that of Bensaude, which is a

beautifully illustrated book on sigmoidoscopy and was published by the same Company some years ago.

The time-honored methods of examining the stomach, namely the history, physical examination, gastric analysis and X-ray study have been supplemented within recent years by two methods, both of which have been immensely improved. These are gastroscopy and gastrophotography. Both of these methods have for their purpose a study of the gastric mucosa; in both instances, earlier attempts were

poor but these later attempts are rich in promise. Gastrosocopy has for its purpose the exploration of the interior of the stomach. It necessitates a concept somewhat removed from the ordinary approach. The stomach to the gastroscopist is a different stomach from that of the radiologist, the clinician and the anatomist. The gastroscopist deals in mucosal patterns. He has a highly labile structure to handle. Local contractions, alterations in tension, changes in color and alterations in the gastric rugae or plications present interesting problems apart from the actual appearance of the mucosa.

This volume discusses the various instruments employed and their method of introduction as well as the appreciation of normal and pathological mucosal changes. Two models of instrument have engaged the attention of this author, the flexible Wolf-Schindler and the rigid instrument of Schindler. The Wolf-Schindler instrument is characterized by an optical system with a series of lenses of short focus, sufficiently close together to permit of movement. The peripheral portion bearing illumination and the superior part both are rigid. The inferior rigid segment is 8 cm. long, the flexible portion 27 cm. and the rigid oropharyngeal is 34 cm. There are, of course, some objections to this instrument. Such an instrument must of necessity be somewhat frail and the complexity of its optical apparatus does not give the clear illumination of the rigid instrument. Furthermore, sterilization in the ordinary way is out of the question. Montier uses a weak solution of oxycyanide of mercury. A discussion of other instruments appears and while mention is made that gastro-photography is possible by means of the apparatus of Henning, the latter is a rigid instrument; we know of no means by which photography can be made part of the study by the flexible instrument.

This volume is a careful *exposé* of all the details of gastroscopy and it bears the additional merit that it is written by a clinician from the clinical viewpoint. No mere gastroscopist could have written this volume and Montier is fully alive to the restrictions and the difficulties attending this method of examination. The idea that gastroscopy is a simple bedside problem is dispelled by the thoroughness of this volume. One gets the impression that gastroscopy is almost an operating room offense. Certainly, careful previous preparation, thorough local anesthesia and the need for several assistants is desirable. The Author frankly discusses the difficulties as well as the dangers of gastroscopy. The dangers, he feels, are markedly alleviated by the use of the flexible instrument. The contraindications which he recognizes are deformities of the vertebral column as well as the chronic sufferers with pulmonary and cardiac diseases, dyspnea and obesity. Pharyngeal diverticula, esophageal strictures, cirrhosis with esophageal and gastric varices, aortic and mediastinal lesions present almost insuperable obstacles and recent gastric hemorrhage is recognized as a definite contraindication. In fact, Montier points out that it is well to abstain from all endoscopic examinations of the stomach for at least a month after a hemorrhage. It is likewise desirable to avoid such examinations if there is fever, violent pain or evidence of any acute gastric condition. Pharyngeal and esophageal lesions might be followed by diffuse mediastinitis and death although the use of the flexible instrument apparently has robbed this procedure of much of its danger. This

Author points out that perforation can even follow X-ray examination and quotes Paneck, who claims that 22.2% of gastric perforations followed X-ray study and that 11.1% were unquestionably due to it; a statement that hardly tallies with the facts which we observed. The preparation of the operator and his education as well as the preparation of the patient, the technic in the introduction of the tube and the general appearance of the normal stomach mucosa are considered in great detail.

Perhaps gastroscopy finds its greatest field of usefulness in the much misunderstood chapter of gastric affections, known as chronic inflammations of the mucosa. With the newer interest in gastritis as a precursor of carcinoma and ulcer the evidence yielded on gastroscopic examination is useful even if not final. Certainly the studies of Hayem, Lion, Loeper, Schindler, and Konjetzny have thrown light on the seriousness of chronic mucosal inflammations of the stomach. Montier recognizes the proliferative form of gastritis showing changes in secretion, hyperplastic inflammation, including the hypertrophic forms going all the way to the so-called "*état mamelonné*," the group which he calls "Gastrites Alteratives" representing changes varying from a simple edema to gangrenous ulceration, in which are included edematous gastritis, hemorrhagic gastritis, ulcerative gastritis and the atrophic forms of gastritis and finally, the form which he calls "Gastrite Segmentaires" all of which are recognized by gastroscopy. This chapter is complete and well worth reading because it includes the clinical approach as well.

The chapter on gastric ulcer is of interest to the clinician; some of the observations are those which only a gastroscopist could make. The larger number of ulcers was clearly gastric and the Author points out that 75% of gastric ulcers are observed along the lesser curvature and the ulcer-bearing area is clearly the lesser curvature and posterior wall. It is surprising to note that the Author has never seen a true ulcer in the antrum. It is true that they are relatively rare, but they do occur. There is an interesting discussion in this chapter on the actual appearance of the ulcer as compared with its radiographic image. An ulcer, on gastroscopy may appear as a lozenge shaped loss of substance, a simple fissure or even star-shaped in form. Owing to the movement of the stomach wall, the tendency for the mucosa to overlap and the crater of the ulcer to become filled, a lesion can be overlooked by this method as well as by X-ray examination. There is no question that small ulcerations, which cannot be revealed by ordinary X-ray study can be demonstrated by both gastroscopy and gastrophotography. We have had this experience on a number of occasions.

We feel that gastroscopy should always be carried out by an expert. If misinterpretations are to be avoided the skilled gastroscopist must have a broad clinical knowledge as well. In our own institution, this work has always been done by the department of esophagoscopy where all the requirements, trained assistants and careful preparation of the patient insures a procedure which is relatively free from risk. There is no question that gastroscopy has come to stay and that it affords an additional diagnostic procedure of the greatest value in certain cases. We believe that in the hands of a tyro, the method can be not only unsafe, but misleading. Those of us who have been interested in gastrophotography have had a somewhat



similar experience. How was it possible to interpret the blurred photographs of several years ago and on that basis submit a patient to operation? At the Jefferson Hospital, after two years with the improved gastrophotographic instrument in the hands of Mr. Falenks, we have changed our minds regarding the value of that instrument, entirely flexible with the exception of the small terminal piece, but the latter procedure consumes less than a minute and is not an operating room procedure. Furthermore, we have gotten excellent photographs of the mucosa representing practically all the types mentioned by Moutier. Gastroscopy, in permitting direct inspection, is even preferable, but on the other hand, a painted picture after gastroscopy is not to be compared with an actual photograph. For that reason, we have used gastrophotography as a routine procedure within the last two years and we have photographs of gastric lesions which were not revealed on X-ray examination. Gastroscopy, when indicated, has been performed by the bronchoscopic department, formerly under Dr. Chevalier Jackson and now under Dr. Clerf's supervision. While biopsies can be performed with a direct vision instrument such as Jackson's, it is out of the question with a flexible instrument (Schindler's) and this is the case with gastrophotography as well.

Montier's discussion of ulcer evolution is one which will interest the clinician and we are glad to say that this Author is not above using every method at his disposal to make a diagnosis. There are many radiographs in the volume. Contrary to the opinion of Konjetzny and Korbach, this Author believes that the true peptic ulcer and an ulcerative gastritis are essentially different phenomena. The behavior of the active ulcer with its irritable stomach is contrasted with the latent ulcer, a point which is borne out by radiographic examination as well. Moutier maintains that it is possible to determine a cure of the lesion and the degree of activity by this means, both of which are of interest to the clinician.

The chapter on cancer of the stomach is one that concerns all of us. Here again, Moutier is dominated by the findings of the laboratory, but he is strong in his statement regarding the current methods which are to be used. He maintains that X-ray study is not a means of early diagnosis, but rather of late diagnosis in cancer of the stomach. We feel that this statement might be put the other way and that is, that late diagnosis is due to the fact that the disease is so silent and latent in the early stages that in the great majority of instances when the patient reaches us, the lesion already is far advanced. Certainly the need for gastroscopy will not be revealed until the patient presents himself for examination and the same delay will then be apparent. A careful description of the findings of gastric cancer is given, revealing the infiltration, alteration in the plications, tendency to tumor formation and alteration of the normal mucosal pattern as well as ulceration. In the absence of biopsy, it is difficult for anyone to say that the localized alteration in the mucosa is necessarily malignant. Here is where Schindler's "closed instrument" fails us in early lesions. Some years ago, we took motion picture photographs of the mucosa of a large series of cases with carcinoma and the variation in the pictures was so great as to make it difficult to reach a definite conclusion from the superficial mucosal picture alone. The same thing is true of gastrophotography. Carcinoma

reveals many alterations in the mucosal pattern. The suggestion is made here as with other methods of examination that, when in doubt, an examination should be repeated within a few weeks to confirm or to deny the finding.

We do not believe that routine gastroscopy will reveal many early malignant lesions that are not revealed by a careful radiographic study by an expert, although one is intrigued with the possibilities of a direct inspection of the mucosa. We feel that in doubtful cases, every method of diagnosis should be used. We should not hesitate to avail ourselves of all of these methods of examination in given cases; but particularly in the question of gastric carcinoma. Those of us who have had much experience with this problem know how difficult the early diagnosis really is. We know the lesion infiltrates, while it may or may not ulcerate or cause changes of mucosal pattern or interferes with peristalsis. We have a number of gastrophotographs which match the various pictures which adorn Moutier's volume, but the problem of early diagnosis is by no means so simple as it would appear from the discussion. There are many alterations of the gastric mucosa which are suggestive and will bear watching, but except in the advanced lesion there are few pictures which are pathognomonic. The reviewer is convinced that the majority of gastroenterologists who are interested in this problem will agree that at least a large part of the failure to diagnose early gastric carcinoma is due as much to the patient and the curious latency of the disease as it is due to the inability on the part of the gastroenterologist to recognize the lesion. In a great majority of instances, the gastric cancer that we see is well advanced and easily recognized by ordinary clinical means.

There need be no hesitation in recommending Moutier's book to all students of this problem. It is well done, worthy of study and the Author is to be congratulated on the method of presentation and the general excellence of his work.

Martin E. Rehfuess, Philadelphia.

An Atlas on Biliary Drainage Microscopy, by B. B. Vincent Lyon, M.D., Philadelphia, Pa. Issued in Limited Edition and Privately Printed and Assembled by the Author. Thirty-Four Pages of Text Supplementing 110 Original Photomicrographs and Photographs. Subscription Price for Each of the 100 Copies to be Available, \$25.00 (United States funds).

ON May 4, 1920, the afternoon train from Atlantic City to Philadelphia carried a half dozen animatedly vocal members of the American Gastro-Enterological Association. On the previous day, under the modest title, "The Need of Early Diagnosis and Treatment of Cholecystitis and Cholelithiasis," they had heard Dr. Lyon present his initial, public announcement of the fact that, by taking advantage of the results of physiological investigations with solutions of magnesium sulphate (studies made by Prof. S. T. Meltzer) via a properly introduced duodenal tube, specimens of the content of the gall-bladder and bile passages could be secured. With conservatism and restraint, from the standpoint of today,—rather more than fifteen years—Lyon described his epoch-making observations and advanced clinical pointings possible from such. The lapse of time, the prompt



objections—*then* even scornful and acid—the researches of scores of physiologists—*then*, extremely incredulous of the work of both Meltzer and of Lyon—clinical studies and a voluminous literature, have added or subtracted little of basic significance from what the proponent of biliary tract drainage, as a diagnostic and a therapeutic procedure, presented in his initial discourse. Indeed, the clinical and laboratory procedure which quite properly bears Lyon's name was, as advanced by him, a clinical method in advance of experimental proof which subsequently—*tho'* not without much controversy and travail—was to demonstrate the function of Oddi's sphincter, the common duct's internal pressure, the ability of the gall-bladder to exhibit "peristaltic" activity, the relationship of the innervation of the biliary system and that of the stomach and other abdominal viscera.

The acumen of Lyon in adapting a procedure from "pure investigative effort" to clinical use was unique fifteen years ago. Similar adaptations now are not uncommon; in fact, one may say that a chief guiding spirit in investigation at laboratories affiliated with our first grade medical schools is that which plans and carries through researches in an effort to solve problems of a clinical character.

The liveliness of the discussion following Lyon's address, combined with a certain incredulity that specimens from the biliary tract actually could be secured for study, *prior to abdominal section*, explains why that group of physicians travelled from Atlantic City to Philadelphia on that hot, dusty—no "air conditioning" in those days!—train. They wanted to observe Lyon's procedure "at first hand": the technique, the type of patient, the material recovered, to study that material, to appraise its significance, to have exhibited to them the results of "duodenal drainage" as therapy. Briefly, they wished "to look over Lyon's shoulder while he worked, and to *be shown!*"

As physicians know—and certainly, Dr. Lyon now well has realized—there are limits of time, patience and physical and brain endurance to that sort of thing. In a comprehensive book, as a teacher, by demonstrations and addresses before representative medical societies, Lyon gave to our profession most generously of his time and energy in explaining, qualifying and elaborating "his" method. This not always was a pleasant task, because seldom in our day has a man and his work been so unjustly or viciously attacked. At once, he was subjected to a storm of criticism by investigators and clinicians, often men who were misinformed, had not performed or had not followed closely the procedure or of Lyon's own findings or interpretations, by captious critics of the "set" type who resent being aroused from smugness, by surgeons or by that group of our profession which doesn't know that it doesn't know, but ever is vocal. However, Lyon has weathered the storm most admirably. The method, which he set forth in 1920, in all modern and though-unshakelled clinics, now in an established diagnostic procedure and, in selected instances—as, for example, where the surgeons already have "had their innings" and the patient still is a "duct and liver invalid"—a therapeutic aid of indispensable value.

Now comes the "Atlas" a stupendous piece of original, specialized effort in which Lyon actually allows progressive clinicians and laboratory workers "to look over his shoulder," to observe, with his interpretation, what can be learned—and depended upon—in that most

important field, *microscopy* of fresh material secured at biliary tract "drainage."

In its *physical make-up* the "Atlas" is unique. Its "text" is brief—approximately 34 pages of multi-graphed, condensed data. This is a veritable "Bible" on the subject, axiomatically terse and pointed, from Lyon's own enormous clinical and laboratory experience. Under proper technical conditions and with controls, supplemented by such records as few men or institutions have compiled—nay, of which actually never have they even thought—the Author has recorded his observations. This text is faced by 110 photomicrographs (there is but a scant half dozen or so schemata and roentgen reproductions), each an "original." These photographs admirably are illustrative of what one who is an expert technician, and who knows what it is that he sees, can find when he makes an intelligent and serious effort at the microscopic study of the alimentary and biliary tract contents when such have been secured via the inlying "duodenal" tube in the upper alimentary tract or metapylorically placed. Below each photomicrograph is a crisp, explanatory legend.

Rarely has our profession been favored by a contribution holding this "here is the proof of things as recorded by the microscope and camera" form of instruction. Such photographic demonstrations actually place the burden of *disproving* Lyon's method of diagnosing pathology—particularly *early* departures from the normal—*via* duodenal intubation, squarely upon the shoulders of its critics. Until contrary evidence is submitted by opponents as skilled in technique and interpretation as is Lyon, very definitely, indeed, must stand his method and his deductions from the microscopic study of *freshly* secured and promptly examined material.

The *text* of this "Atlas" opens by drawing a timely analogy between what, several decades ago, diagnostically, constituted kidney or urinary passage disease from data available at examinations of the urine—*late* disease then—and what, since microscopy (and chemistry) is stressed, *now* constitutes the diagnostic findings—data which give us indications of *early* urinary system disease. Similarly, less than twenty years since, diagnosis of biliary tract disease came from recognition and evaluation only of facts derived from patients' histories and from physical examinations and meant but appreciation of *advanced* lesions. Indeed, apart from the recognition of malignancy and the cirrhosis, until the advent of "explorative" abdominal section and particularly since the introduction of the duodenal tube, as a diagnostic aid, what we now know as biliary tract disease, was regarded as only *gall-bladder* pathology. Those familiar with the subject will recall with this reviewer, that so recent as approximately ten years ago (even after Lyon and others, by employing the duodenal tube as a diagnostic aid some years previously, definitely had shown that but few instances of gall-bladder pathology are unassociated with gall-duct and liver changes) the contribution of Pratt and Stengel stressing how chronic affections of the gall-bladder and ducts are capable of causing such advanced pathology as cirrhosis of the liver, proved an important influence in establishing among internists (*tho'* not so widely among surgeons) that gall-bladder disease alone—in the presence or the absence of calculi—

rarely exists. This reviewer finds no mention of Lyon's work in Pratt and Stengel's contribution.

Briefly, but succinctly, Lyon discusses—and illustrates—often in the form of *axioms*, the significance, as shown by microscopic study, of what may be present in specimens secured through the duodenal tube. The normal and the abnormal are detailed in a most word-sparing summary. Emphasis is placed upon the recognition of cellular structures, bacteria, food remnants, parasites and crystalline formations in regards to *local* segments of the alimentary and biliary tracts: the oral cavity, the oesophagus, stomach, duodenum, gall-ducts, gall-bladder, etc. From an unusual experience, controlled by careful records and made permanent by photomicrographs, the Author is able very decisively to establish certain criteria which, in the form of "axioms," mean to him not alone evidence of pathology but, by his methods, to *localize* that pathology and to gauge its degree in the regions considered. Lyon expresses well his ideas and, at perhaps a slight sacrifice of certain details, from his observations derives such "axioms" as "Excess cellular exfoliation means irritation of the mucous membrane of the zone from which such epithelial cells are derived"; "Increased pus cells mean inflammation"; "No unbile-stained epithelial cells recovered in duodeno-biliary aspirates can be considered derivable from liver, gall-bladder or bile ducts"; "Excess bacteria, freely distributed or in colony formation, mean infection, etc."; "A bacterial colony cannot be considered derivable from the biliary tract unless it is bile-stained"; "Increased *mucus* means *catarrh*"; "Excess *crystals* in a biliary tract drainage-sediment mean *formed* or *forming* gall-stones," and so on. Each "axiom" is elaborated upon from the viewpoints of error in observation, in technique, as to its pathologic significance and its diagnostic value. Thus, in very small space, Lyon presents a condensation of what is and has been helpful to him clinically from a systematic, microscopic examination of more than 280,000 "drainage" returns. It is upon this enormous material that the Author has built the foundations of his widely-known clinical and laboratory procedure. That he is justified in his employment of metapyloric, tube "drainage" of the biliary tract, diagnostically and therapeutically, seems well established. Certainly those of Lyon's critics who have worked amateurishly or have condemned his procedure upon second- or third-hand data, secured not alone from few patients but by unskilled or non-medical "assistants," should give pause to their vocalizings in the face of facts and so great a material examined and controlled over more than fifteen years.

Lyon includes in his discussion the very important observations that, in affections of the oesophagus, stomach and duodenum, expert microscopy of "wet," fresh material obtained *via* the duodenal tube, proves of valuable service in the diagnosis of both early and late lesions of those segments of the alimentary tract. Undoubtedly, with less inconvenience to the patient and without the employment of "test-meals" likely to confuse microscopic examination, and without the introduction of annoying, large "stomach" tubes, Lyon's procedure is worthy of wider appreciation and employment than is common. Examination of "fasting" contents for the recognition of cellular structures, bacteria, etc., long has seemed to the reviewer to be of importance far greater than is "tubing" with the object of determining "acidity" and ferments—factors

which now we know widely fluctuate even in digestively sound persons (recently so strongly emphasized by Hellebrandt, *American Journal of Digestive Diseases and Nutrition*, September, 1935, page 402).

The text section of the "Atlas" concludes with a thorough discussion of the recognition and the significance of parasites, crystals and food particles recovered at tube "drainage" and detected by microscopy. The pages devoted to this subject alone are invaluable, particularly as long experience has shown to the reviewer that, all too often, even so-called "experts" pass lightly over the meaning of residues of the class mentioned or they fail entirely to recognize what the residues are!

The *illustrations* constitute, perhaps, the most valuable part of Lyon's "Atlas." Certainly, the collection, grouping, assembling, mechanical effort and the devising of legends to fit both text and pictures must have been a soul-trying task. It is an achievement, technically, which excites one's enthusiastic congratulations to the Author. It was this collection of photomicrographs, when shown in the Scientific Exhibition at the 1935 Convention of the American Medical Association, which is responsible for the issuance of the "Atlas." So great was the interest in Lyon's demonstration and so persistent were the demands by physicians who visited the exhibit that *somewhere, somehow*, what Lyon had accumulated be made available to others for leisurely study and for their guidance, that the "idea" of issuing the photomicrographs with explanatory text, was conceived. That the difficulties to be overcome were formidable was recognized, as also was the fact that since no publisher would undertake such highly specialized work, the Author and his assistants wholly must be relied upon. This meant that, in whatever form these photomicrographs became available, of necessity, the output definitely must be limited—especially if each "print" was to be an "original" and each picture must be placed in any "book" by hand. The required financial outlay seemed prohibitive when it was considered that but few books could be issued.

However, with characteristic ingenuity, patience and hard work, Lyon overcame the seemingly impossible. The result means the issuance of approximately only 100 "Atlases" but assures also that whoever becomes the fortunate possessor of a copy, has at hand, unquestionably, the finest and most complete collection of photomicrographs of material secured from the upper alimentary tract and from the gall-bladder and biliary passages, as yet, extant. So beautiful and instructive are these pictures that we venture to prophesy that, for many years, reproductions of them will appear in standard texts or in books concerned with special phases of gastro-intestinal and biliary tract disease. Apart from the value of these photomicrographs, as they elucidate the text of this "Atlas," each very readily could be reproduced as a lantern-slide and the whole, in such fashion, would form a collection of very great value in the instruction of medical students and of laboratory workers.

It is not possible by words to describe the beauty or the comprehensiveness of these photomicrographs: they must be seen and studied if one is to realize, adequately, their technical perfection in a most difficult field, their instructiveness and too, the tremendous amount of effort which, personally, the Author must have been compelled to give to the selection of the

original specimens, the grouping to serve his purpose, their arrangement in association with legends and text and, finally, to completeness in the field discussed. Although Lyon, himself, has had several hazardous experiences with the abdominal surgeons, one may not contemplate this "Atlas," the latest of his numerous important ventures into medical authorship, without feeling strongly, that whatever the surgeons may have done to him, they did not deprive him of his "intestinal fortitude." The reviewer has scrutinized critically each of the photomicrographs in this unique collection and has been unable to find a "poor" one. What this means will be appreciated by those who have attempted photomicrography with "wet" specimens—mostly unstained—when we mention that the illustrations include epithelia, salivary corpuscles (and of *lecithin liberated from such!*), myelin threads, pus cells, various bacteria, algae, bile-duct "casts," crystalline formations, protozoa (wonderful groups of giardia), (some perfect at  $\times 1600!$ ), strongyloides, and practically every common form of food cell. Even if there were no "text," Lyon's "Atlas" would be a monumental achievement.

Doubtless, this work will serve as a model for the issuance of similar volumes, particularly in specialized fields of endeavor. To the reviewer, publications of this character sorely are needed, especially by physicians and investigators who have "passed the first grade." More than ever, what is desired (as did the Members of the American Gastro-Enterological Association who travelled to Philadelphia on that hot day in May, 1920, to "look over Lyon's shoulder") is fewer huge textbooks whose contents have been assembled from many sources by the plugging, but rarely brilliant, type of "author," but more and briefer texts which represent

what one clinician or investigator has found he can depend upon—and such books actually planned and written by that person. Our shelves are laden with what purported to be the "latest and most authoritative" and yet, on examination, proved "just another compilation"—hence, remains decorative, perhaps, but rarely used. Our money outlay for that kind of book runs into startling dollar-figures: when we "pass on," the volumes rarely sell for as much as twenty-five cents each, if at all! The crying need in medical literature is for books which bear the stamp of personality, individual effort, first-hand knowledge, pioneering, usefulness, and which do not attempt to cover so much ground that one knows, instinctively, that not even a Nicholas Senn could have been sufficiently versatile as to have been "an authority" on so many varied topics.

Lyon has given us a "path finding" book, every page of which bears the stamp of personal effort, careful and controlled clinical and laboratory experience and conservatism, yet sufficiently daring to venture into what, seemingly, will be common knowledge a decade or two hence and, above all, a series of illustrations which demonstrate the unquestionably valuable discoveries of his pioneering.

Whatever may be the cost of this type of book, always it will be worth what one pays. The regrettable feature is that an "Atlas" such as that of Lyon's must be an issue limited as to number available. Fortunate, indeed, is he who secures a copy!

Frank Smithies.

N. B. The reviewer paid the full price: he would have felt it an imposition had he accepted an "Atlas," gratis, "for review." Also, he would have regretted that by so securing a copy, one person would have lost the opportunity of buying one.

## SECTION XI—*Societies, Programs and Proceedings*

### Report on the First International Congress of Gastro-Enterology Held at Brussels, Belgium

THE Belgian Society of Gastroenterology has been in existence for some years; likewise the periodical the "Journal Belge de Gastro-Enterologie." About a year ago, largely through the activities of Dr. Georges Brohée, a gastroenterologist in Brussels and the Editor of the Journal, the interests of these were pooled and the International Congress was born. The officers and Honorary Presidents representing the various countries were selected and contacts were made with prominent men throughout the world. The Presidents of the different gastroenterologic societies, 22 in number, were appointed as "Patrons." As part of Belgium's activity in connection with the national exposition, the occasion was propitious for congresses of various kinds to be held in Brussels. Dr. Brohée was

the moving genius and organizer to establish one on gastroenterology, which was held in Brussels, August 8th to 10th inclusive under the presidency of Dr. Jan Schoemaker of The Hague.

With the exception of nearby France, the largest delegation from any foreign country came from the United States. Most of these came from the Eastern part of the country, the South and West not being represented. In this country propagandic work for the Congress had been going on for some months. At the last moment, the United States appointed a committee of 9 all of whom were members of the American Gastroenterological Association headed by a retired Army Medical man who was an otolaryngologist. Representing the two national gastroenterological or-

ganizations here, there were 17 from the National Society for the Advancement of Gastroenterology, 5 from the American Gastroenterological Association, 3 who belonged to both organizations, and 10 who belonged to neither of them: all together 32 Americans.

The Committee of Organization consisted of five members. These met with committees of like kinds from different countries, formed a permanent organization, adopted statutes, and selected Paris, France, as the place of the next Congress to be held in 1937. The official languages selected were English, French and German.

At Brussels no American had been selected for the main papers; 5 entered into the discussions. The subjects considered were Gastritis and Ulcerative Colitis. It being the first congress, run without a permanent organization and with no guiding experience, there were omissions in the way of arrangements for exhibits, unbalance in representations, absence of interpreters, etc., but no doubt these will be provided for in future Congresses. The enthusiasm and spirit however ran high and the Belgian medical men displayed themselves as excellent social hosts to the visiting medical men and their ladies as well. The American authorities most mentioned in the papers read and the discussions were Doctors W. Beaumont, W. J. Mayo, M. E. Rehfuess, M. Einhorn, H. Bockus, A. Basler, J. Bank, F. D. Ackerman, E. B. Benedict, W. Allen, R. H. Cheney, C. C. McClure, B. Crohn, E. S. Judd, G. W. Nagel, A. B. Rivers, I. W. McRoberts, M. E. Steinberg, W. Alvarez, Lynch and Felsen, M. Paulson, A. Borgen, M. Rosenou, and S. Flexner.

In this country with the advent of abdominal surgery, roentgenology, bacteriology, etc., we have gotten away from an interest in gastritis as a subject. This has not been so with the European gastroenterologists, and since Minot and Murphy's work, attention to deficiency disorders, and the possible connection of gastritis with ulcer and carcinoma, real attention to gastritis has been reestablished here. The use of the Wolf-Schindler flexible gastroscope has added stimulus to this.

Dr. A. F. Hurst of England, drew attention to the exceptional frequency of chronic gastritis, the inflammatory changes seen in ulcerated stomachs, suggested that chronic gastritis may be an underlying cause of carcinoma, the importance of alcohol and the continuous use of purgatives as particularly important in the causation of chronic gastritis, the significance of "elimination gastritis" from products administered outside of the stomach, the relationship of gastritis in the production of diseases of the liver and gall-bladder, and the significance of gastritis occurring after gastric operations due to invasion of bacteria into the anacid remaining portion of stomach.

Prof. H. H. Berg of Hamburg, brought out the limited value of the X-ray in the diagnosis, in which relief changes, severe and deformed, plastic thickness due to hypertrophy and oedema and non-malignant neoplastic rigidities were important. Hypertrophy of the rugae, he believed, was only of value when accompanied by constant changes, that spasms were largely the result of swelling states, and that great care and considerable experience were necessary so as

not to suspect a carcinoma when only a gastritis was present.

Dr. Francois Moutier's of Paris, contribution on the anatomic pathology of gastritis was exceptionally able especially in the micro-pathology. He showed the frequency of the acute, subacute and chronic processes existent at the same time in various parts of the same stomach, the occurrence of epithelial erosions, the differing pathology of the glands, and the associated degeneration of all the structures that make up the stomach as an organ. He held that hypertrophic reactions of the epithelial cells of the lining or acini are less common than believed, that the mucosa tends to change by localized necrosis and fibrosis, that the gross appearance of the mucosa in diagnosing hypertrophy or atonic states should not be made without histological study and this ruling in the use of test meals as commonly studied, the X-ray and the gastroscope.

Prof. Lion of Paris, discussed the value of test meal examinations from the standpoints of the volume of secretion and concentration abilities especially in connection with the hormone excitants of gastric secretions and enzyme values in diagnosis. He scheduled the values in functional and syndrome states and the ease by which the chemism can be altered by various agents such as medications, various functional and emotional disturbances even for long periods of time.

Prof. G. E. Konjetzny of Hamburg, presented the surgical aspects of the subject. In this he drew attention to the symptom-complex of gastro-duodenitis being non-recognized and often diagnosed as ulcer and that gastro-duodenitis requires distinctly more study and attention than is being paid to it. He believed that surgery in chronic gastritis should be confined to localized polypoid swelling of the mucosa in which there is suspicion of malignancy and to the various forms of non-malignant hypertrophic stenosis which in the large majority of cases are sequelae to chronic gastritis. Another paper on the surgery of the subject was presented by Dr. H. Paschoud of Lausanne, which summarized the entire subject of gastritis.

Prof. F. G. Mones of Barcelona, presented the pathology in connection with Prof. P. Domingo Sanjuan who added the bacteriology of ulcerative colitis. Their beliefs were that this disease was toxic-infectious in etiology in which the most important offender is the streptococcus. While attaching importance to the Rosenow-Borgen so-called "diplostreptococcus," which they found commonly in healthy intestines, from its action on haemoglobin, cultural characteristics and bio-chemical qualities, they claim is identical to the *streptococcus mitis*, it being only a secondary variety according to the classification of Brown's. While these organisms and the majority of the diplostreptococci found in ulcerative colitis have a pathological effect on rabbits, in healthy individuals they are innocuous. It was claimed that, when in the very occasional human, they produced lesions it was by effect on the mucosal chorin, the lesions not being in any way characteristic of the disease. Currettings of the mucosa of patients with ulcerative colitis and the intravenous inoculations of salt solution filtrates made with a Chamberland L (3) filter produced a disease in rabbits similar to the inoculations of pure cultures. They therefore felt, as

Bassler had drawn attention to, that a filterable virus may be the cause of the disease, a virus that may at times be found in healthy individuals. They stated that their experiments very much diminished the value of the conception that the diplostreptococcus is the only cause of the disease. Judging by analogy of *B. tuberculosis* injections in Guinea pigs, the anaerobic organisms are enhancers of virulence. They concluded their presentation with the following statement: "The treatment is not very successful and until now we cannot do much more than work against the symptoms; a specific treatment does not exist." Prof. I. Snapper of Amsterdam, claimed that the causative agent was unknown even though a typical clinical picture of the disease exists. He felt that any form of treatment, including the biologic, should not be viewed optimistically, rest in bed, strengthening, and easily digestible diets with heat on the abdomen being the most worth while. He cautioned against believing in the curative effect in the use of drugs, lavagings and vaccines, and that almost all cases in which the ulceration is limited to the rectum and descending colon have a good prognosis under any form of treatment—thus the cure of such a case cannot be regarded as proof of the efficacy of any particular drug or method. When the right colon is definitely involved no method has much effect, this explaining why the collaboration of the surgeon is so often required.

The paper of Dr. Dall'Acqua of Milan, was an excellent presentation of the X-ray diagnosis of ulcerative colitis especially in the roental studies of the early cases, for only in this way can the inflammatory alterations of the colon in the mucosal substratum be revealed. In this the reactional contractions of the muscular layers and the auto-plasticity of the mucosa occur in a way which gives definite roentgen patterns. He brought forward that different radiological pictures are seen in the same case at different times and different in various parts of the colon and different in the same part according to the influence of functional changes; this explains why one may have anything from the absence of classic pictures to the different characteristic pictures met with in the certain cases. He felt that characteristic pictures meant serious involvement.

Dr. B. Vintrup of Copenhagen, stated that the disease was first described by Wilck and Moxon in their lectures on pathological anatomy (London, 1875) and but little has been added to their original description of it. He drew attention to the denuded coats of the mucosa and submucosa being replaced by naked granulation tissue and claimed that the disease is primarily an affection of the mucosa involving chiefly the blood vessels and the connective tissue with masses of leucocytes at the edges of the ulcers, a zone of fibronoid necrosis, congested tissue containing polyblasts, and the mucosa rich in fibrocytes and fibrils but no conspicuous sclerotic processes. In the slow and chronic case the *muscularis* remains well preserved for a long time, but in the fulminating case it becomes quickly involved.

Prof. R. Goiffon of Paris, advanced that blood in the movements was the first stool finding and that modifications of the blood and urine are secondary and are the result of complications rather than due to the ulceration itself.

Prof. M. Donati of Milan, made the point that there were different forms of the disease, and that infectious and surgical conditions in different parts of the body (teeth, sinuses, gall bladder, etc.) should have attention in these cases. He felt that the various types of direct surgery were dependent upon the study of the case at hand and that total colectomy should be rejected. He believed in conservative surgery if it sufficed and that one should not be partial to any standard way or a single surgical procedure for all cases, some not doing well with ileostomy but far better with colostomy on the ascendans, transverse or even the left side. He preferred doing a right colectomy in one stage but using several stages on other parts of the colon.

These papers were discussed by 130 persons. Because of the small time possible, each discussion was so short that it was unsatisfactory especially so with the mixture of languages spoken. Since French was the dominant language of the Congress the discussion was rendered further unsatisfactory by the poor and hesitant French that most of the foreigners struggled with. The writer suggests to those who attend the future Congresses that they be familiar with French but speak at the medical meeting in their native tongue. Generally it was true that those who attended this Congress understood English and were anxious to hear it spoken. They would far rather have this, than be treated to a poor quality of their own language some of which must have been far more difficult for them to understand than would have been English. It should be stated that the Europeans deeply appreciated the large and representative delegation that came from the United States. It is to be hoped that one day this Congress will be held in this country and that we be given the opportunity to repay our Belgian hosts for the kindnesses extended to us.

Anthony Bassler, New York City.

---

DELEGATES ON THE PART OF THE UNITED STATES TO THE FIRST INTERNATIONAL CONGRESS OF GASTRO-ENTEROLOGY APPOINTED BY THE DEPARTMENT OF STATE, UNITED STATES GOVERNMENT  
Brussels, Belgium, August 8 to 10th, 1935

---

Lieutenant Colonel John H. Trinder, Chairman, Medical Corps, Retired, United States Army.

Dr. Henry L. Bockus, 250 South 18th Street, Philadelphia, Pennsylvania.

Dr. Russell S. Boles, Rittenhouse-Plaza, Philadelphia, Pennsylvania.

Dr. Max Einhorn, 20 East Sixty-third Street, New York, New York.

Dr. Sara Jordan, 605 Commonwealth Avenue, Boston, Massachusetts.

Dr. B. B. V. Lyon, 2031 Locust Street, Philadelphia, Pennsylvania.

Dr. William Gerry Morgan, 1801 Eye Street, Washington, D. C.

Dr. De Witt Stetten, 850 Park Avenue, New York, New York.

Dr. Franklin W. White, 322 Marlboro Street, Boston, Massachusetts.



REPORT ON THE ANNUAL SESSION OF THE  
AMERICAN PROCTOLOGIC SOCIETY,  
JUNE 10, 1935

The Atlantic City meeting was the largest in the history of the Society with a total of 218 members and guests present. 70% of the Fellows and 64% of the Associates attended the sessions.

The following Associates were elevated to Fellowship:

Dr. Jesse Hall Allen, Philadelphia.  
Dr. James Kerr Anderson, Minneapolis.  
Dr. Harry E. Bacon, Philadelphia.  
Dr. Karl Brucker, Lansing.  
Dr. Emor L. Cartwright, Fort Wayne.  
Dr. A. W. Martin Marino, Brooklyn.  
Dr. Frederick G. Smith, Philadelphia.

From a very large group of applicants, the follow-

ing were selected for Associate Membership in the Society:

Dr. Hulett H. Askew, Atlanta.  
Dr. Hugh Beaton, Fort Worth.  
Dr. F. B. Bowman, Hamilton, Ont.  
Dr. E. A. Daniels, Montreal.  
Dr. Geo. F. Eubanks, Atlanta.  
Dr. Benjamin Haskell, Philadelphia.  
Dr. E. J. Lynch, Detroit.  
Dr. S. D. Manheim, New York.  
Dr. W. J. Martin, Louisville.  
Dr. J. P. Nesselrod, Rochester, Minn.  
Dr. John C. Noss, Altoona.  
Dr. R. A. Scarborough, San Francisco.  
Dr. M. S. Woolf, San Francisco.

The 1936 meeting will be held in Kansas City in conjunction with the A. M. A. next May. Dr. Frederick B. Campbell will be Host to the organization at that time. Kansas City, in the heart of America, is accessible to all portions of the country and there is every prospect of a splendid attendance.

Curtice Rosser, Secretary, Dallas.

## ABSTRACTS

HINTON, J. WILLIAM, AND CHURCH, REYNOLD B.

*The Incidence of Gastrojejunal Ulcer Following Gastro-enterostomy.* S. G., and O., 60:65-73, Jan., 1935.

During the five year period beginning Jan. 1, 1928, the Gastro-Enterological Clinic of the Fourth Division of Bellevue Hospital admitted 583 cases of peptic ulcer, 143 of which had been previously operated upon. Of this latter group 79 had had gastroenterostomies and 13 of these patients (16.4%) presented marginal or gastrojejunal ulcers. The reports of these 13 cases are adequately and concisely presented by the authors. One patient had two gastroenterostomies performed and developed a marginal ulcer after each operation. Another patient who developed a marginal ulcer after a gastroenterostomy submitted to a gastric resection and yet 1½ years later showed another marginal ulcer. The authors' plea for a ten year follow-up is endorsed by the fact that in three of the cases symptoms did not develop until seven years or more after the operation. They attach little dependence upon a follow-up letter because of the periodicity of symptoms presented and prefer a frequent personal examination. Conservative medical treatment is recommended as long as it affords symptomatic relief. Continued severe pain generally means perforation into some adjacent viscus and is therefore the chief indication for operation. Six of the 13 patients reported required operation of some type. The medical treatment used included the Sippy routine, gastric mucin, Saunderson's streptococcus vaccine, intravenously, and in one case aolin, subcutaneously.

J. Duffy Hancock, Louisville.

WILBUR, DWIGHT L., AND OCHSNER, HAROLD C.

*The Association of Polycythemia Vera and Peptic Ulcers.* Ann. Int. Med., Vol. VIII, p. 1667, June, 1935.

After a review of the literature on the association of polycythemia vera and peptic ulcers, beginning with the first report published in 1905 by Weber and Watson, to 1934, when Boyd reported a case, the authors summarize by stating that not all writers have been able to concur in the opinion that duodenal ulcer and polycythemia are frequently associated. Doubt as to the accuracy of the diag-

nosis of polycythemia vera in some of the cases covered by the literature is expressed, the belief being entertained that some of them were cases of concentration polycythemia or polycythemic hypovolemia. Reference is made to a suggestion that both of these diseases appear to be a result of disturbance in secretion of epinephrine, that polycythemia is relative or secondary to a loss of fluid and that duodenal ulcer associated with hyper-secretion results in an excessive production of an intrinsic hematopoietic factor and that the occurrence of ulcer is a result of a thrombosis of blood vessels in the mucosa of the stomach and duodenum. In all, the authors studied 143 cases of what they termed proved polycythemia vera, the basis for such proof being elevation of the erythrocyte count and the hemoglobin content above normal values, increase in viscosity and volume of the blood and a hematocrit reading indicating a higher percentage of erythrocytes than the normal value of 45 to 48 per cent. Patients represented in the group were closely observed over a considerable period, hence the opportunity for discovering gastro-intestinal symptoms was considered good. In another group of 143 cases 1114 gave no history suggestive of gastro-intestinal disease; 17 cases were subjected to roentgenologic examination of the stomach and duodenum and no pathological process was disclosed; in 12 cases there were roentgenologic or pathologic evidences of peptic ulcer. The ulcer was located in the duodenum in 10 of these cases and in the stomach in 2. Of the 10 duodenal ulcer cases one was diagnosed at post mortem, 9 were demonstrated by X-ray examination. In 7 cases the history of ulcer antedated the history of polycythemia vera by periods varying from one year to 21. Singularly, of the two cases with gastric ulcer, one gave no history suggestive of ulcer, the lesion being an accidental finding post mortem. In the other case symptoms had obtained for four years and polycythemia symptoms for about two. The study of the acidity contents of the stomach in patients of the group with polycythemia disclosed that of the 24 cases so studied only one showed a marked increase in hydrochloric acid. Four cases showed moderate increases, 16 had acid values within normal limits and 4 had low or



no free hydrochloric acid. In all cases of polycythemia without ulcer high acid values were not found. The authors comment on the problem of a relationship between changes in the gastric juice and an elevated red cell count. Attention is called to the variation in incidence of healed or active ulcers discovered at post mortem, the figures ranging between 10 and 20 per cent. They thought that the incidence of ulcer of the stomach or duodenum in cases studied for all classes ranged between 2 and 3 plus per cent. In the group of proved *polycythemia vera* studied by the authors, 8 per cent showed X-ray pathologic evidence of peptic ulcer, but inasmuch as all of their patients with *polycythemia vera* were not studied to determine the presence of ulcer, an accurate estimate of percentage of the association of the two diseases cannot be made. The authors suggested that *polycythemia vera* may belong to a group of diseases including tumors of the brain and spinal cord, diseases of the prostate, chronic nephritis, chronic cholecystitis and diseases of the thyroid gland in which gastric and duodenal ulcers are more frequently seen at necropsy than other conditions. On account of the relationship that exists between the secretion of certain constituents of gastric juice and the activity of bone marrow, interest is expressed in the speculation that disturbances of gastric function may be of importance in either the production or the continuation of *polycythemia vera*. They conclude with the statement that there seems to have been little to support the hypothesis that production of an excessive amount of hematopoietic factor may be responsible for increased formation of red cells and that repeated loss of gastric juice by removal has resulted in a decrease of the red cell count. Neither were they able to determine with definiteness the relationship of thrombosis of duodenal vessels to the development of duodenal ulcer in patients with *polycythemia vera*, though the tendency of polycythemic blood to form thrombi is well known.

Virgil E. Simpson, Louisville.

WADHAMS, R. P., AND CARABBA, V.

*Electrosurgical Aseptic Intestinal Anastomosis. S., G., and O., Vol. 60, No. 6, pp. 1082-1092, June, 1935.*

The authors present the experimental technique, pathological physiology and some suggestions as to the application of aseptic intestinal anastomosis by electro-surgical methods.

The intestinal loops to be anastomosed are approximated by a seroseros continuous suture of 20 day No. 00 chromic catgut. With the bipolar electrode attached to a 1000 millampere coagulation current the tissue is coagulated along a line parallel to the line of suture. The coagulation points must enter the intestinal wall about 1 centimeter away from the line of suture; they should begin about 1½ centimeters proximal to the ends of the suture line. The tissue between and around the coagulating points turns white and then pale grey in color indicating that the optimum point of coagulation has been reached. The coagulated areas are apposed by several Lembert sutures of plain catgut and the seroseros suture completed around the anastomosis. After seven days the coagulum has sloughed away, the anastomosis is functioning and healed. The line of anastomosis usually contracts about one-third of its length.

Specimens studied at 24, 48, 72 hours and 8 days after operation showed that the slough had separated after 48 hours; the edges of the anastomosis showed healthy granulation after 72 hours. In 8 days the mucosa is completely regenerated throughout the anastomosis.

The authors have used this method in making anastomoses between the duodenum and the colon, and between various other parts of the intestinal tract in the dog. In one case they successfully anastomosed the ureters to the colon in the dog.

They propose the operation for all types of side-to-side anastomoses as done in man, and particularly in the obstruction type of resection of the colon in which operation

this procedure done at the time of the first operation will obviate the necessity of applying the Mikulicz clamp later. Nine figures accompany the article.

N. M. Percy, Chicago.

REES, C. E.

*Anterior Gastro-enterostomy by the Short Loop Method. S., G., and O., Vol. 60, No. 6, pp. 1125-1128, June, 1935.*

The author presents a short loop method of anterior gastro-enterostomy which offers the advantages of the posterior gastro-enterostomy and avoids some of the disadvantages of the classical anterior operation.

The gastro colic ligament is cut near the greater curvature of the stomach and the transverse colon is elevated above the stomach. An avascular area in the transverse mesocolon is located and incised sufficiently to allow room for the anastomosis. The edges of the incision in the transverse mesocolon are sutured to the anterior wall of the stomach and the anastomosis made between that area in the stomach and the uppermost part of the jejunum. After the anastomosis is completed the colic side of the gastrocolic ligament, first detached from the stomach, is sutured to the anterior wall of the stomach. The abdomen is closed without drainage.

Three figures accompany the article.

N. M. Percy, Chicago.

GEORGE DE TARNOWSKY, M.D., AND P. JOSEPH SARMA, M.D., Chicago, Ill.

*The Surgical Treatment of Chronic Pancreatitis. Annals of Surgery, June, 1935.*

The authors state that a bare generation ago, chronic pancreatitis was considered a rarity—or its entity denied by internists. Opie taught that its symptoms were so indefinite as to make it impossible of preoperative diagnosis intra vitam. As clinicians began to grasp the all important fact of the close interrelation which exists between the liver and its biliary tract on the one hand, and the pancreas with its ducts on the other, dysfunctions of the latter organ began to assume greater importance.

In disturbances of a gland having such varied and all important functions as has the pancreas one would—a priori—be justified in assuming that clinical revelations would be many and almost pathognomonic. Unfortunately, the only two striking clinical manifestations are fat necrosis and pancreatic hemorrhage, both present in the severest of cases, both demonstrable only at the time of surgical intervention. The authors analyze 30 cases of chronic pancreatitis, illustrating the extreme difficulty of making a positive preoperative diagnosis.

Clinically, the authors divide pancreatic dysfunction into three main groups:

(A) Disturbances of external secretion interfering with the digestive apparatus in the subacute or chronic types, or producing autolysis in the fulminating cases of pancreatic apoplexy.

(B) Disturbances of internal secretion leading to glycosuria.

(C) Carcinoma of the head of the pancreas.

The authors feel that direct continuity to gastric or duodenal ulcers plays an occasional role as an etiological agent in chronic pancreatitis, and they believe that repeated, subsiding attacks of pancreatitis are, at least in the vast majority of cases due to the entrance of bile into the pancreatic duct or ducts and that as long as normal bile from the gall bladder is discharged thru the common duct into the duodenum, no pancreatitis will result. As other positive etiologic factors, they mention arteriosclerosis, cysts or tumors of the pancreas, alcoholism, tuberculosis, syphilis, hemochromatosis and hepatic cirrhosis.

In dealing with symptomatology and the difficulty in establishing a diagnosis of pancreatic pathology they quote J. W. Hinton, "The pancreas is the only intra-abdominal

organ that produces symptoms of a chronic surgical nature that physical examination, roentgenologic or laboratory studies will not aid in establishing a diagnosis except by negative findings."

The authors state that cholecystostomy with prolonged drainage is the operation of choice in chronic pancreatitis—thus agreeing with Gask, Mayo-Robson, Moynihan, Cammidge, Gosset, Petit-Dutallis, Hartman, Hey-Grove, Deaver, Finney, Horsey, Archibald, Cecil, Osler and others who make the same recommendation.

They also advocate choledochotomy to relieve the pancreatic dysfunction in cases where there are valid indications for cholecystectomy.

Charles T. Sturgeon, Los Angeles.

BIALOCK, A.

*Experimental Studies on the Effects of the Perforation of Peptic Ulcers.* S., G., and O., Vol. 61, No. 1, pp. 20-26, July, 1935.

The author performed experiments designed to determine the factors which are responsible, in the main, for the early severe signs and symptoms of perforation of ulcers. Bile, pancreatic juice, gastric juice, and duodenal secretions were obtained by cannulating the various structures. Those juices were then injected with a syringe and needle into the peritoneal cavities of other dogs, and the effects noted.

The following results were obtained: (1). Following the injection of large amounts of one or more of the upper intestinal juices, the animals became ill almost immediately. (2). The injection of sterile pancreatic juice in large amounts produced very little reaction. Infected pancreatic juice in smaller quantities caused death. (3). The injection of bile produced immediate and severe reactions, but only one died. The reaction to bile was much more severe than that to pancreatic juice. (4). A mixture of bile and pancreatic juice causes a reaction more severe than the same quantity of either juice alone. (5). Quantities of gastric or duodenal secretions equal to those of bile injected did not cause death in any of 9 experiments. (6). All of the animals, which died as a result of the introduction of one or more of the secretions, exhibited marked reddening of the intra peritoneal structures. When mixtures of pancreatic juice and bile were injected there was massive fat necrosis. Large amounts of free fluid were found in the peritoneal cavity at autopsy, but that quantity alone was not sufficient to account for the marked decline in blood volume at time of death. (7). The earliest major changes in the cardio-vascular system following the injection of bile and pancreatic juice were a drop in blood pressure and later, a marked drop in the cardiac output.

The author feels that the early circulatory failure may be classified as vasogenic, while the later stage is mainly hematogenic.

N. M. Percy, Chicago.

ROSSER, CURTICE.

"Cancer of the Anal Canal." *South. Med. Jour.*, 28:527-530, June, 1935.

General opinion locates the majority of rectal cancers in the ampulla but the author believes that most will be found to originate in the narrow rectosigmoid canal where the bolus enters the rectum or in the narrow anal canal where it leaves. In a study of 75 cases of rectal cancer, he found that 23.3% of the growths apparently had their origin in the anal canal. In the 25 cases of cancer of the anal canal where biopsy and follow up observation were attainable, 84% were found to have an associated benign pathological lesion—fistula, hemorrhoids, polyp, or cryptitis—which in the majority of the cases was believed to be primary with the malignancy developing at least partially as a result of long continued irritation.

The outstanding symptoms of cancer in various parts of the colon are described and differentiated, the character-

istic symptom of cancer of the anal canal being localized pain which is not true of growths elsewhere in the colonic tract. In spite of this and the accessibility of the lesion, the patients in this series came for treatment rather late. The end results were not satisfactory, due in part to the delay in diagnosis and in part to insufficient radical surgery. It is suggested that more careful attention be given to complaints of "rectal trouble" and that treatment should consist of wide resection rather than radiation alone or with local excision.

J. Duffy Hancock, Louisville.

ERB, M. B., AND FARMER, A. W.

*Ileocolitis.* S., G., and O., Vol. 61, No. 1, pp. 6-14, July, 1935.

The authors report and discuss four cases of a form of ileocolitis, heretofore not described, characterized by marked edema of the terminal ileum, ascending colon and Peyer's patches. Clinically, the condition is indistinguishable from acute appendicitis. At operation the appendix is found to be normal, while the ileum and colon with their mesenteries are engorged and solidly edematous. Post-operatively the patients run a course characterized by persistent fever (up to 100.4 degrees F. in cases terminating favorably), some distention of the abdomen, and malaise. In cases terminating unfavorably the temperature rises to 104 to 106 degrees F. and a clinical picture simulating intestinal obstruction develops.

This condition is recorded as a new entity and its differences from other similar affections of the intestinal tract pointed out. From some of the cases the authors recovered an organism called *Bacillus H*, which showed positive agglutination reactions with the area of most of the patients tested. While the etiology of this condition is obscure, the authors feel that it may be a phase of the condition called "chronic cicatrizing enteritis" or "regional ileitis."

N. M. Percy, Chicago.

J. A. BARGEN AND E. T. LEEDY.

*Carcinoma of the Rectum.* *J. A. M. A.*, 104:1210, April 6, 1935.

Two hundred patients with carcinoma of the rectum were interviewed by the authors. The purpose of the study was to find out the reason for the poor prognosis in rectal cancer.

Ninety-two patients had consulted a physician within a month from the onset of symptoms. The others waited from two to twenty-four months after the onset of their trouble and until their own treatment had failed, before consulting a physician.

The earliest symptoms in the whole group were bleeding, then pain, then constipation and lastly diarrhea. Most patients had combinations of these complaints.

Self medication was the rule among these patients. Diet, constipation remedies and "pile" cures were resorted to.

Rectal examination was not made by the first physician consulted in many of the cases. The patients in many instances objected to such an examination or the physician did not wish to hurt the patient. In many instances palliative treatment gave relief and the patient did not ask for further examination and care.

Therapy was further delayed because of the hopeless attitude with which operations for rectal carcinoma have been regarded.

Results from operation for rectal carcinoma will improve as patients consult physicians earlier, also with more widespread employment of the digital examination among physicians and as knowledge spreads as to the safety and satisfactory results from operative intervention.

Francis D. Murphy, Milwaukee.

# CANNED FOOD IN INFANT NUTRITION

## II. Strained Foods

● During the first few months of life, breast milk or modified cow's milk, properly supplemented, is the major article of food in the infant dietary. In later infancy and early childhood, however, it is desirable that other foods be included to supply the increasing demand for food essentials in which the milk diet is inherently deficient.

Modern practices in infant nutrition, while similar in broad aspect, may differ in detail. The first addition to the supplement milk diet is usually that of cereals or cereal broths. Later, strained vegetables and fruits, valued for their contributions of iron and cellulose materials, are included. Finally, other foods, such as egg yolk, broths and soups, are added to the dietary at the discretion of the physician.

Especially designed and well suited for use in this phase of infant nutrition are the canned strained foods. Manufacturers of such products are mindful of the fact that the highest possible standards as to quality and food values must be maintained—that endorsement or acceptance of these products by the profession can be obtained only after actual trial. Consequently, precautions are taken in the commercial procedures to retain in as high degree as possible the quality characteristics and nutritive values of the raw products used.

Only selected materials at the proper de-

gree of maturity enter into the manufacture of commercially strained foods. Within a few hours of harvesting, the raw products are subjected to preparatory operations such as cleansing, peeling or trimming. After preliminary heat treatments, the materials are strained through screens whose interstices are measured in the thousandths of an inch; filled into cans and the cans sealed, heat processed and cooled.

In the canning procedure a number of factors are favorable to the retention of certain fugitive food values. Among these may be included the use of selected, properly matured raw stock; the rapid handling of the harvested crop; the use of steam or a limited amount of water in preliminary cooking operations; the exclusion of air during pre-cooking and straining; the straining of the foods in the liquid in which they were cooked; and the heat processing in sealed containers from which most of the atmospheric oxygen has been removed.

Research has demonstrated that these factors operate effectively in the retention in high degree of food values in the canned strained products (1). Consequently, commercially strained foods or food combinations—readily available on every market—deserve a high place among foods adapted to infant and child feeding, not only from the standpoints of economy and convenience, but by virtue of their nutritive values as well.

## AMERICAN CAN COMPANY

230 Park Avenue, New York City

(1) Journal Nutrition 8, 449 (1934)  
Journal American Dietetic Association 9, 295 (1933)  
Journal Pediatrics 6, 749 (1932)

*This is the sixth in a series of monthly articles, which will summarize, for your convenience, the conclusions about canned foods which authorities in nutritional research have reached. We want to make this series valuable to you, and so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles.*



The Seal of Acceptance denotes that the statements in this advertisement are acceptable to the Committee on Foods of the American Medical Association.

## SECTION XII—"The Clinic"

### Unusual Causes for Symptoms of Biliary Tract Disease, With Case Reports

By

J. W. THOMPSON, M.D., F.A.C.S.  
ST. LOUIS, MISSOURI

STATISTICAL reports of end results in the treatment of diseased abdominal viscera frequently cause one to lose sight of the individual patient. The clinician, searching through columns of tabulated "percentages" is frequently disappointed and has a distinct sensation of inadequacy when he fails to find some assistance in the solution of a special case problem. An interchange of related case reports around a luncheon table often will provide the needed enlightenment which is notably lacking in the perusal of columns of figures. That master clinician, George Dock, once remarked to a group of students on a ward walk: "There are no diseases, only people who are sick." The student of statistics of end results compiled by the questionnaire method frequently has little comprehension of the actual status of individual trees in his forest of figures. The family physician or consultant "back home" is the more capable interpreter of end results after a period of observation sufficiently long, properly to evaluate therapeutic benefits. Therefore, the report of clinical observations on individual cases covering a long period of time would seem to be of some value.

There is no physician or surgeon who has not been plagued by the individual patient who did not get well and remain so following a surgical procedure. This is particularly true in the field of abdominal surgery, especially so in operative procedures on the biliary tract. "Operation can only be held responsible if the improvement persists for a period of years or if it becomes permanent"

(1). The amount of benefit generally corresponds to the degree of pathologic change in the involved organs. Synhorst (2) in a series of 300 cases presented data admirably substantiating this conclusion. Poor results were noted in 33.3%, four cases having minimal pathologic change. Even in cholesterosis of the gall bladder, the so-called "strawberry" might, in the mind of a patient who was unbenefited, be justifiably metamorphosed to "raspberry." In distinct contrast are the 93% good results in cases of marked pathologic change.

The causes of persistence of symptoms following cholecystectomy may be briefly enumerated as follows: stones in bile ducts, hepatitis, cholangitis, pancreatitis, trauma to the ducts with subsequent stricture, adhesions. The last mentioned item covers a multitude of excuses and "adhesions" have plagued both physician and patient from the beginning of history in abdominal surgery. It is only recently that the research of Ochsner and Garside (3), Trusler (4), and others had begun to throw some helpful light on the problem. Lacey (5) concluded that amniotic fluid concentrate does no harm but he was not convinced of definite benefit through its use. The experiments of Ochsner and Garside, based upon the work of Walton (6), who prepared a trypsin-papain combination, demonstrated in animals the value of the principle of injection of substances intraperitoneally in prevention of postoperative adhesions.

The following two cases are considered to be worthy of report because of the unusual nature of the conditions which were believed to have been the cause of the symptoms.

Sufficient time has elapsed since the operative procedure to justify the conclusion that to the operation in each case could be attributed the relief obtained by the patient.

*Case No. 1.* E. S. A spinster, aged 38. Came to this Clinic in February, 1929. Her complaint at that time was attacks of general abdominal pain more severe on the right side, and relieved by vomiting. The attacks were quite incapacitating and had occurred so frequently that she had been unable to follow her work as a milliner since 1920.

The patient's past history was of great interest. She had survived the usual childhood illnesses without complication. She had, however, in her adult life undergone numerous surgical adventures. In 1922, her hemorrhoids were removed and a uterine displacement corrected. She remained well for a year and another abdominal operation was done to remove a fibrous growth around her colon. Following this procedure she did not get along so well; required enemas of oil to relieve constipation. In 1926 she had been examined by a roentgenologist who diagnosed "colon trouble with gall stones." Again she submitted herself to surgical intervention and in November, 1926, the gall bladder was removed and abdominal adhesions "broken up." She recovered, but the attacks of abdominal pain accompanied by nausea and vomiting occurred at increasingly frequent intervals. She presented herself to us for relief.

Physical examination of the patient was of little help. She was already a battle-scarred veteran of several surgical campaigns. A careful study was made of her psyche in order to eliminate the possibility of

a "dyed in the wool" surgical neurosis, but after numerous interviews with the clinician and psychiatrist it was conceded that the patient was not the victim of neurosis or a malingerer.

Clinical laboratory studies were undertaken in the interim and may be briefly summarized as follows: Counting of blood cells. Wassermann, gastric analysis, examination of urine and stool, basal metabolic rate, and blood sugar estimation. All gave values within normal limits. Food allergy tests—not significant.

Roentgenologic examination of the stomach and intestines elicited the following information:

1. Evidence of adhesions about the duodenum.
2. Stomach emptied in five and three-quarter hours.
3. Strikingly atypical small intestinal loops.
4. Twenty-four hour ileal stasis.
5. Obstruction of the ileum, kink, highly characteristic of post-operative adhesions. Definite narrowing at point of obstruction with marked dilatation of the small intestine proximal to kink. There was definite tenderness over the cecum.

Cystoscopic examination and ureteral catheterization did not reveal any cause for slight urgency complained of by the patient.

Diagnosis: Partial Intestinal Obstruction and Constipation.

After a period of two months observation and study under careful dietetic and medical regimen without definite improvement, with some trepidation surgical intervention to relieve the obstruction was suggested to the patient. After careful thought she was reluctantly willing to submit, urged a bit by an attack of cramp-like pain accompanied by nausea and vomiting.

Operation—St. Lukes Hospital, April 18, 1929.

Pre-operative diagnosis: Partial intestinal obstruction.

Low-right rectus-muscle splitting incision. There were three distinct points of partial obstruction in the terminal ileum; the first being at the brim of the sacrum; the second to the right ovary; and the third deep in the pelvis, adherent to the pelvic colon. These areas were carefully dissected free and the raw areas covered with sterile olive oil (7, 8) in the hope of prevention of new adhesions

and points of obstruction. Exploration of the upper abdomen disclosed dense adhesions in the right upper quadrant binding all structures together.

*Subsequent course:* The patient's symptoms were relieved. The attacks of nausea and vomiting ceased. Post-operative roentgen examination of the gastro-intestinal tract revealed normal pattern in the small intestine which have been shown in illustrations of a previous paper (9).

Her nervous system suffered some shock due to the sudden cardiac death of her father shortly after her dismissal from the hospital. Since the same accident had befallen a favorite older sister, this event was interpreted as a possible cause of pain in the right upper quadrant which came in quite alarming attacks requiring mid-night visits and administration of hypodermic of morphine to give relief. There was vomiting of bile associated with the attacks, a slight elevation of temperature of 99.6° to 100° F.; a leucocyte count of 10,000; and on one occasion a faint icteric tint to the sclera. The attacks, so the patient stated, were almost identical with

## An Atlas on Biliary Drainage Microscopy

By

B. B. Vincent Lyon, M.D.

This album contains thirty-eight pages of explanatory text and one hundred and twenty photomicrographs of the various objects observed microscopically during a biliary drainage as part of the clinical study of selected patients.

The photomicrographs demonstrate exfoliated epithelial cells from the mouth, esophagus, stomach, duodenum and gall bladder; various types of mucus indicating catarrh; bacterial colonies indicating infection; crystals, suggesting gall stones; some of the upper intestinal and biliary tract parasites; and various food "rests" observed in gastric or duodenal stasis.

A considerable portion of the text is devoted to a description for their easy recognition, for their diagnostic interpretation, and for their clinical application. Such microscopy has often puzzled the well-informed, as well as the novice in gastro-intestinal work.

Each atlas is literally an original copy; attractively bound in black leather and is offered to a limited number of subscribers for educational purposes such as medical schools for student instruction; hospital or private laboratories for training of technicians in biliary drainage microscopy; or to such doctors as may be interested in gastroenterology.

Anyone interested in securing a copy at a price of \$25.00 plus postage charges may do so by mailing the following slip.

.....  
Dr. B. B. Vincent Lyon.  
2031 Locust Street,  
Philadelphia, Pa.

I wish to subscribe for ..... Atlas on Biliary Drainage Microscopy. Kindly mail by insured parcel post, to

Name ..... Address .....

Please note: Because each Atlas is made up by hand as an original copy, delivery cannot be made earlier than four months from receipt of order.

Check for \$25.40 must accompany order.



## TOXIC CONDITIONS

may be the organic trouble occasioning apparent symptoms in the gastrointestinal tract.

It is highly important to treat the effects of the gastrointestinal troubles adjunctly with the proper treatment of the Toxic Conditions. This is best accomplished through Bile Salts Therapy in the administration of

## TAUROCOL Bile Salts Tablets

*Clinical Record Forms for the asking.  
Samples and information on request.*

**The Paul Plessner Co.**

Detroit - - - Michigan  
J. D. 11-35

## TILDEN HAS KEPT FAITH WITH PHYSICIANS

## MALTOPEPSINE (Tilden)

*For Prescription in Alleviating Digestive Distress and as a Vehicle for Administering other Therapeutic Ingredients*

Composition: Dioscorein, Lactic Acid, Diastase and Pepsin balanced with other ingredients in a manner exclusive with Tilden. **DECIDEDLY PALATABLE — RAPID RESULTS — ECONOMICAL**

### Gastric and Intestinal Upsets

For many years physicians have prescribed the specialties of The Tilden Company more than any others in the ethical pharmaceutical field, because Tilden has always kept them under the exclusive control of the medical profession.

Our Medical Information Department will be honored by physicians' requests. Inquire for the New Calberon tablet of Buffered Gluconate, adjunct to Maltoprepine.

## The Tilden Co.

*The Oldest Pharmaceutical House in America*

New Lebanon, N. Y. St. Louis Mo.  
A. J. D. D. 11-35

those she suffered before the removal of her gall bladder.

Thereupon, after consultation with the clinicians, again including a psychiatrist among them, surgical approach to the solution of the enigma was elected.

**Operation:** Operation on September 20, 1929, under ethylene anesthesia through an upper right rectus incision, disclosed a mass of dense adhesions with a complete distortion of all anatomical relationship. The round (falciform) ligament together with the duodenum was adherent to the lower costal margin. The duodenum was quite densely attached and twisted as a torque, pulling up the mid-portion of the common duct (Fig. 1). After careful dissection, freeing the adherent structures from one another, the common duct was explored. Clear bile found. No stones were discovered in the biliary ducts. A thin small Penrose drain was placed above and a second one below the gastro-hepatic ligament and her abdomen closed without further exploration. Immediate post-operative recovery—uncomplicated.

**Subsequent course:** The patient's symptoms were relieved and she remained well until September, 1930, when it became necessary to do a diagnostic D. & C. to rule out a possible malignant condition of the uterus as a cause of intermenstrual bleeding; microscopic examination of the uterine scraping was negative.

During the intervening five years the patient has been under frequent observation. She has had no more severe attacks, her complaints being those of minor ailments. The function of the colon has been only fair. She requires lubrication and an occasional saline cathartic to control constipation. She has entered into the menopause and symptoms of hot flashes are readily controlled and diminished in severity by the administration of ovarian hormones.

During the interim, the patient has been exceptionally cooperative—has carried on her work as private secretary to a minister, and in the opinion of the author, is not a sufferer from neurosis. There was an organic basis for her symptoms which have been relieved by a combined medical and surgical regimen covering a six year period of observation.

**Case No. 2.** Mrs. F. W., aged 42, housewife. Came to this Clinic

August 25, 1929. Her complaints were abdominal pain generalized but more severe across the upper abdomen. The pain was almost constant and had no direct relationship to meals or food. She had been slightly jaundiced one year prior to admission. Her appendix had been removed because of an acute attack. The surgeon had told her the operation was very difficult, due to her obesity, and required two hours to perform it.

**Family history:** She is the mother of a son who is a typical case of pituitary adiposity.

**Physical examination:** Entirely negative except for the observation that she was of the hypersthenic type with a suggestion of ovarian and pituitary obesity (weight 217, height 5'-6").

Clinical laboratory examination revealed normal condition of her blood (including Wassermann), complete blood counts, blood sugar. A cholecystogram produced no shadow of the gall bladder.

A diagnosis of cholecystic disease was made, possibly with stones obstructing the cystic duct. Operation was advised after medical management failed to relieve her symptoms during an attempt of ten months duration.

**Operation:** May 9, 1929. Cholecystectomy was performed under gas-ether anesthesia. The patient had been operated elsewhere previously when a transverse upper abdominal incision was made. A new longitudinal muscle splitting incision was made. Dense adhesions were encountered between the abdominal wall and the hepatic flexure, the colon and the falciform ligament. The gall bladder was kinked under torsion about 3 c.m. from the fundus with a definite point of constriction caused by pressure from the liver edge. The gall bladder in the proximal two-thirds was almost completely surrounded by lobulation of liver tissue (Fig. 2). This condition apparently produced definite pressure upon the gall bladder during the process of filling. The liver in the region of the gall bladder was moderately scarred from chronic hepatitis. The stomach and duodenum were normal in appearance and to palpation. The pelvic organs were normal. The abdomen was closed around a small Penrose drain placed in the liver bed formerly occupied by the gall bladder.



*Subsequent course:* The patient made an uneventful post-operative recovery and has remained entirely free of all symptoms for the past several years.

#### DISCUSSION

The first patient is an excellent illustration of the difficulties encountered by the clinician and surgeon in the management of those people who are not relieved of their symptoms by one surgical procedure. The patient in his misery frequently goes from one medico to another until his resources are exhausted or until he can no longer find a sympathetic ear. Psychiatrists are apt to sneer at the futile efforts of internists and surgeons to relieve such people, attributing their symptoms to some vague neurosis. Since the ascendance of the science of allergy, the surgeon must be even more cautious lest he be guilty of placing his indelible marks on the virgin abdomens of those who are possibly sensitive to everything from wheat to seal fur. Consequently it is of vital importance to conduct an extremely careful diagnostic search in those patients who have been subjected to abdominal surgical procedures and failed to find the promised relief. The services of clinician, surgeon, roentgenologist, psychiatrist, allergist, and spiritual advisor may need to be enlisted. On the other hand it requires great courage mixed with common sense to advise repeated operations when success is lacking after the initial attempt at relief. The gratitude of those patients who are finally relieved of their symptoms and restored to useful activities is balm to the ego sufficient to soothe the pangs of regret induced in the clinician whose advice occasionally proved to be wrong. There is no field of medicine or surgery requiring closer cooperation of various specialists with astute observation on the part of each than in the management of the patient who was not benefited by operation. Wisdom is required lest conditions are aggravated by ill-advised attempts to remedy the difficulties allegedly brought about by our surgical predecessors in their efforts to obtain a desirable end result. The permanent benefits derived by the cases presented in this report, after

a period of more than five years of observation, seem to justify reporting them in the hope that the diagnosis of "surgical neurosis" be not made without careful clinical studies and cooperative observations.

#### REFERENCES

1. Judd, E. S. et al: *Practice of Surgery*. Chap. 2, Vol. VII.
2. Synhorst, A. P.: Quoted by Judd. *Ibid.*
3. Ochsner, Alton and Garside: S., G., and O., 54:335-361, Feb., 1932.
4. Trusler, H. M.: "Peritonitis, Experimental Studies of Healing in the Peritoneum and

- Therapeutic Effect of Amniotic Fluid Concentrate." *Proc. Staff Meeting, Mayo Clinic*, 4:356, Dec. 11, 1929.
5. Lacey, J. T.: "Prevention of Peritoneal Adhesions by Amniotic Fluid." *Ann. Surg.*, 92:281-293, August, 1930.
6. Walton, R. P.: "Papain preparation suitable for Prevention of Adhesions." *Proc. Lac. Exp. Biol. and Med.*, XXXVIII, 1922, 1931.
7. Crump, W. G.: "A New Oil in Treatment of Post-Operative Adhesions." *S., G., and O.*, XLI, 491, 1910.
8. Martin, A.: "Ueber die an derselben person wiederholte Laparatomie." *Zeit für Geburts- u Gynecol.*, 1888; XV: 293.
9. Soper, H. W., and Thompson, J. W.: "Adhesions of the Small Intestines." *Am. Jour. Surg.*, Vol IX, No. 2, 243-250, 1930.

### *The World's Most Famous Natural Alkaline Water*

## PRESCRIBED BY PHYSICIANS THE WORLD OVER

VICHY CÉLESTINS, the most famous of natural alkaline mineral waters, is indicated in stomach and liver affections and digestive disorders in general; in gout, arthritis associated with uric acidemia, uricemia, and nephrolithiasis of uric acid origin. During convalescence, it eases and expedites the journey back to health. Vichy Célestins is obtainable everywhere.

BOTTLED ONLY AT THE  
SPRING IN VICHY, FRANCE



# VICHY CÉLESTINS

Write for booklet on Therapeutic Value of Vichy with Medical Bibliography.  
AMERICAN AGENCY OF FRENCH VICHY, INC., 198 Kent Ave., Brooklyn, N. Y.

## ABSTRACTS

LEITHAUSER, DANIEL J., AND CANTOR, MEYER O.

*Lugol's Solution in Acute Secondary Parotitis. Annals of Surgery, Vol. 101, No. 5, May, 1935.*

The authors remind us that although acute secondary parotitis is a rare complication occurring in .03 per cent of a series of cases reported by Pique in 1907, in .04 per cent of cases reported by Beckman from the Mayo Clinic, and in .75 per cent of 135 cases of operations on the colon and rectum by Rankin and Palmer, never-the-less it is very important in that about a 50% mortality is recorded for it.

The authors give brief case histories of ten patients with acute secondary parotitis to whom they gave Lugol's Solution in large and repeated doses by mouth and by hypodermoclysis in saline with beneficial results. They gave from 15 to 20 minims every three hours over a period of from three to eighteen days.

They state that they were prompted to adopt this therapy knowing the beneficial effects of antiseptics which are eliminated through the kidneys in urinary tract infections and knowing that iodine is promptly and rapidly eliminated by the parotid gland.

Of the ten cases reported and treated with Lugol's Solution there were no deaths and only two went to abscess formation, one of which was drained thru incision and the other by repeated aspirations through a large calibre needle.

Charles T. Sturgeon, Los Angeles.

HENRY A. RAFSKY, New York.

*Injection Treatment of Peptic Ulcer (With Special Reference to the Use of Histidine Monohydrochloride). Med. Record, Vol. 142, No. 6, pp. 289-292, Sept. 18, 1935.*

Rafsky reviews in a critical way the experimental work on dogs by Weiss and Aron in which the deviation of the duodenal secretions into the lower end of the ileum regularly produced ulcer, two to four weeks after operation. Other findings resulting from the experimental operation were anemia, diarrhea and strong acidification of the intestinal contents. Weiss and Aron presented their theory of peptic ulcer, based on an amino-acid deficiency. The experimental ulcers were treated by daily injections of a mixture of histidine and tryptophane and proved cures regularly resulted. Eventually it was found that histidine itself was responsible for the favorable effect and consequently the tryptophane was eliminated.

Histidine is now available under the trade name of larostidin and consists of 5 c.c. ampules of a four per cent specially prepared iso-tonic solution of levorotary histidine monohydrochloride,

which is adjusted for intramuscular injection.

Rafsky used the larostidin treatment on 26 cases. He is very careful not to employ the word "cure," since his patients were under observation for only about 4 months and he considers a period of 5 years observation necessary before speaking of actual cure. The treatment is ambulatory, quick in action and requires relatively little dieting. Twenty-four of his cases were duo-

denal, one gastric and one marginal. Symptomatic relief occurred promptly in 73.3 per cent. The patients who did not respond were those with penetrating duodenal ulcer and niche deformity. Marked diminution of acidity almost to the point of anaecidity occurred in 25 per cent of the cases. Pain was alleviated in comparatively short time. Improvement is accompanied by a definite gain in weight.

Beaumont S. Cornell, Fort Wayne, Ind.

## Viabie Bacteria Reduced To Zero (Or Near Zero)

In 15 series of samples of the defecate from a number of human subjects. The subjects were not injured by the medication, as determined by thorough clinical and laboratory examinations immediately after cessation of medication and for a number of months subsequent thereto.

The medications employed were two saponaceous glycerites of Alpha Naphthol designated:

## ALPHA NAPH CO AND JELLY OF ALPHA NAPH CO

The Alpha Naph Co was taken in water and orange juice. The "Jelly" was administered in enteric coated capsules opening in the intestinal tract.

A resume of the reports, and adequate supplies for clinical test, will be gladly sent to any physician interested, with our compliments.

**CAREL LABORATORIES**  
REDONDO BEACH - - - CALIFORNIA

## SECTION I—*Clinical Medicine: Diseases of Digestion*

### The Experimental Study of Visceral Disease<sup>\*</sup>

By

DR. MARTIN E. REHFUSS

and

DR. GUY M. NELSON

PHILADELPHIA, PENNSYLVANIA

**T**WENTY-FOUR years ago one of us was impressed by the presence of visceral infection following the experimental injection of various pathogenic organisms into laboratory animals. In a relatively large series of animals, dead of bacterial infections, many forms of digestive pathology were noted. Some eight years ago, through the facilities of the Frankford Foundation for Medical Research, we were able to institute a study of the effects of ordinary pathogenic organisms encountered in visceral disease and their effect on laboratory animals.

The two groups of organisms which interest the gastro-enterologist are the colon group and the streptococcic group. The colon bacillus is of interest to every student of digestive pathology. It has been demonstrated that closely allied types of colon bacilli are normal inhabitants of the intestines of most lower animals. We all realize that this organism has its normal habitat in the large bowel but we are also impressed with the fact that the colon bacillus can be the subject of widespread pathology. Medical literature is full of references as to the ability of the colon bacillus to produce disease. Colon Bacillus Septicemia, discussed by Merry; *B. Coli* Sepsis by Keefer; *B. Coli* Pyemia by Enright and Baugher; Meningitis and Pyelitis are described by numerous authors while its significance in pernicious anemia is pointed out in communications by Whichels, Lucksch, Cohn. That it may induce renal lesions is discussed by Helmholtz; gastric ulcer by Turck; cholecystitis by many authors and the same holds for appendicitis. The presence of the colon bacillus in the infant's stomach is mentioned by Pilosker and Rosenbaum; *B. Coli* in the small bowel by Bernheim and in the Digestive Tract by Tinozzi; while the importance of the colon bacillus in the urinary tract is attested by innumerable references on this subject in the literature.

Our attention has been called to this organism principally because it is found so frequently in the bile of duodenal intubation. We began our study with the aid of Crellin and Edson by studying four strains of the colon bacillus. These strains were isolated and prepared for us by Dr. Crawford, pathologist of the

Jefferson Hospital. *Strain A* came from a gall bladder removed at operation. *Strain B* came from the stool of a healthy individual. *Strain C* was obtained from colon bacilluria and *Strain D* from a case of colon peritonitis.

We immediately injected a series of animals with these four strains of organism and found *Strain A* to be far the most toxic. *Strain B* was less toxic but could kill the animal. *Strain C* was much less toxic so that it was practically impossible to kill a rabbit. *Strain D*, while undoubtedly toxic, was less so than *Strain A*. *Strain A* killed six animals in twenty-four hours and the *B. Coli* was found in every organ. *Strain B* killed only four in twenty-four hours and there was no septicemia, the organisms being found only in certain organs. *Strain D* killed five in twenty-four hours and the *B. Coli* was found in all the organs examined.

The most interesting thing about this series of observations was the difference in toxemia in animals of a given body weight. We then continued to use *Strain A* for our studies. At the end of three months, after the continual passage of *Strain A* through rabbits, this organism was able to kill the animal in a little over two hours. In other words, at the end of the summer, after *Strain A* had gone through more than 200 animals, 2 c.c. of this strain would uniformly kill animals weighing 800 Gm. in a little over several hours. One of the striking findings was the almost explosive effect of this strain on the stomach, producing hemorrhage and even perforation. If, on the other hand, the dose was sublethal the organisms were almost always found in the biliary tract on the one hand and the urinary tract on the other. If the larger dose was given, septicemia was the effect. When we injected a group of animals with this organism in much smaller doses the localization of the organism was almost invariably found in the biliary tract, liver and kidneys. The same thing was true when the organism was injected into the mesenteric system.

Another interesting experiment was to inject these organisms into the gall bladder. The organism was then invariably found in the duodenum but all cultures of the surrounding liver tissue were entirely negative for the presence of the organism. With more than 300

<sup>\*</sup>Read before the 38th Annual Session of the American Gastro-Enterological Association, Atlantic City, N. J., June 10-11, 1935.  
Approved by the Publications' Committee of the Association.

animals we were able to demonstrate the overwhelming tendency of all forms of this colon bacillus to strike the biliary tract, liver and kidneys. We were unable to produce chronic gastric ulcers, but with the highly virulent strain which killed rapidly, severe necrotic lesions were obtained in the stomach. We tried all forms of immunity but were unable to produce an immunity against this strain with dead organisms. On the other hand, we were able to produce by very small, graduated doses, an immunity which was sufficient to withstand the lethal dose of this organism in its most virulent form and cause a total disappearance of the organism in practically every organ in the body. In other words, Edson and Crellin, were able to obtain in their second series, by small, graduated doses of the living colon bacillus, immunity sufficient to withstand a dose which has been proven lethal for a rabbit of given body weight. Furthermore, it is apparent that this immunity is associated with some mechanism by which the colon bacillus is effectively combatted so that these immunized animals killed two days after the administration of a lethal dose fail to reveal the colon bacillus in every organ of the body which we ex-

| ORGANISM               | Pos. | Neg. | Pos. | Neg.  |
|------------------------|------|------|------|-------|
| <i>B. Coli</i>         | 5    | 7    | 4    | 5     |
| <i>B. Proteus</i>      | 1    | 2    | 1    | 2     |
| <i>B. H. Coli</i>      | 1    | 1    | 0    | 0     |
| <i>Strept. H. Coli</i> | 2    | 2    | 1    | 1?    |
| <i>Strept. H. Coli</i> | 2    | 2    | 1    | 1?    |
| <i>S. H. Coli</i>      | 4    | 66   | 13   | 7 11  |
| <i>Strept. H. Coli</i> | 1    | 8    | 2    | 3 (2) |

Fig. 1

amined. Edson and Crellin were able to demonstrate agglutinative phenomena.

We then studied the colon bacillus from the standpoint of the complement fixation tests such as has been elaborated by Burlbank, Kolmer and others. For this purpose we used seven different antigens. It is hardly necessary to go into the details of these studies except to say that the colon bacillus gave a positive reaction in 141 consecutive cases. Antigen 6 gave 88 positive, 37 negative. Antigen 8 gave 103 positive, 35 negative. Antigen 9 gave 119 positive, 19 negative. Antigen 11 gave 121 positive, 15 negative. Antigen 29 gave 120 positive, 10 negative. Antigen 32 gave 91 positive, 38 negative. Antigen 56 gave 66 positive, 19 negative. We studied these seven antigens with 52 cases of cholecystitis, the majority of which gave rather strongly positive reactions but in the control group of 19 cases, an almost equal number of positive reactions was obtained. The striking findings from the complement fixation tests, and we employed three methods in performing this test, was the fact that a certain individual reacted only to certain antigens. The large number of positive antigens argued against the value of this test but, on the other hand, the behavior of the blood serum of a given individual to respond only to certain antigens, strongly suggested that there were inherent differences in these colon groups.

Over the last five years we have had prepared 11 different colon antigens for skin testing and the same phenomenon was noted, namely the very large number of individuals who respond with a positive skin reac-

tion to colon antigens. This has been repeatedly stated in the literature. What is not apparent from this study however, is the frequency with which certain individuals show a marked skin reaction to certain strains in contrast with others. It is this peculiar behavior of the digestive invalid to respond differently to colon strains which suggests strongly the importance of investigating this problem more thoroughly.

Some of our experiences have been rather unique. One of us isolated a colon bacillus from biliary drainage and another, from the urinary tract, in the same patient. Separate vaccines were made from this patient of identical strength. The injections of the colon vaccine from the duodenum produced marked reactions in the cardio-vascular system with tachycardia and arrhythmia while the vaccine from the urinary tract produced a reaction in the urinary tract.

We used more than 300 animals for our colon studies but were unable to consistently produce with sublethal doses, a definite form of organic pathology. Certainly there was no preponderance of ulcer, cholecystitis, joint lesions, cardiac or renal disease. On the other hand the lethal dose produced some of the most pronounced acute digestive pathology that we have seen. We found that some of the colon strains showed slight changes in heat resistance and also alterations in growth on culture media to slight changes in the pH of the media. There is no question however as to the frequency of positive complement fixation tests and severe skin reactions in many digestive invalids who have nothing but colon stasis. The streptococcal problem is a much larger one because so many authorities have ascribed chronic, visceral infection to the activity of these groups.

We sent one of our technicians away for the summer of 1928 with the express determination of finding out how we could separate the pathogenic from the non-virulent streptococci. After passing the summer in two centers of advanced bacterial research, this lady informed us that the only way we could demonstrate or prove that streptococci were pathogenic was to inject them into laboratory animals. We then began a systematic investigation of streptococci from all available sources, injecting them into the rabbits, a strain of which we had at the Institute. To date we have used over 1300 rabbits, most of these being used for the injection of various strains obtained from every available focus in digestive invalids. Cultures of the nose, throat, teeth, sinuses, duodenum, bowel wall, feces and urine have been used.

To enumerate in detail these studies would require far more space than we have at our disposal. We began by taking the cultures of 41 strains of streptococci obtained from the throats of the patients in the Wards of the Jefferson Hospital. We were anxious to obtain a strain which would produce a typical ulcer of the stomach. This was our original purpose. We did produce various visceral lesions but we were unable to produce with any degree of uniformity, a gastro-intestinal lesion. We were able to produce gastric ulcer, cholecystitis in a relatively few cases, lesions of the intestinal tract, but the overwhelming majority of lesions were those confined to the joints, heart and kidneys. This work was largely done by Knox, Edson and Crellin under the direction of one of us. Of the first 41 strains obtained only five were definitely pathogenic for rabbits. One strain was extremely interest-

ing and this we called strain 24. This strain was recovered from the cervix of a woman with puerperal sepsis. It was again recovered from the uterus of the rabbit and it had an undoubted affinity for the joints, heart and kidneys. It was a hemolytic streptococcus. When we first studied this strain it produced arthritis in three weeks in laboratory animals. At the end of the summer, three months later, this strain produced an arthritis in about seven days. During that particular summer we used again some 300 animals and finally used this strain alone in an attempt to produce immunity. We attempted immunity in several ways: One—with the subcutaneous autoclaved vaccine. Two—with the subcutaneous living vaccine. Three—with the intradermal living vaccine. Four—with the intradermal, autoclaved vaccine. Five—with the Besredka skin

other words, we were able to obtain a group of antigens which were fairly successful in bringing about chronic cholecystitis and in the majority of instances we were able to recover the organisms from the gall bladder wall. It was apparent, both from the studies of the literature on the excised gall bladder at the operating table where every precaution was taken, that 45% of the gall bladders carefully studied revealed one of these groups. Furthermore, it is equally interesting to note that no one group is responsible for this lesion. We would point out particularly that these lesions were chronic lesions and not the subacute hemorrhagic lesions characteristic of acute cholecystitis. In a number of instances the lesions required six months to one year before they were produced. Intestinal lesions were by no means constant although instances of severe colitis and enteritis were noted. It is only fair to point out that in these studies, embracing 1300 animals, the commonest lesion encountered was arthritis. Cultures from gastric ulcer at operation, revealing the viridans streptococcus, failed to produce experimental ulcer in our hands. The suggestion that a positive streptococcic complement fixation test is evidence of the bacterial causation of peptic ulcer does not agree with our experience.

We prepared a large number of antigens from streptococci from various sources of proven infection. The number of positive reactions, both with the Burbank method and the modified Kolmer method in human beings was as great in the control non-ulcer cases as it was in those individuals proven to be suffering from peptic ulcer. We spent 1½ years investigating the possibilities of the streptococcus complement fixation tests and our own conclusions scarcely bear out the diagnostic value which we had so hopefully sought. The end reaction of the Burbank test is sharply defined and his technic, as well as the Kolmer technic, were followed exactly. We obtained many positive reactions to the ulcer group and to many other varieties of digestive pathology but we made it a rule to test carefully as many control individuals in whom we could reasonably rule out such lesions as cholecystitis and peptic ulcer. With minor exceptions there were as many positive reactions in the control group as there were in those showing advanced organic pathology. While the number of individuals, 141 in all, is too small to draw an adequate conclusion we believe that anyone who has had experience with this method of testing will realize the multitude of antigens that are possible and will be confronted by an array of evidence which is scarcely conclusive. We have given up this method of testing because of the great frequency of positive reactions in control cases with every form of antigen that we used. The skin tests, or the antigens used intradermally, we believe to be more suggestive and at the same time more valuable. The reaction to the colon group, as we have mentioned, is almost universal but there are distinct differences in the reaction of the individual to the various colon antigens. Positive reactions to the different members of the streptococcic group are far less frequent and to our mind far more suggestive. Cutaneous hyper-sensitivity to many of the streptococcic group is not at all uncommon and when pronounced we believe is of diagnostic import. On the other hand, we feel that the most valuable method of all is to culture consecutively all possible avenues of infection and this we have done clinically for many years. We consider any organism but the

### PERCENTAGE OF GROSS LESIONS.

|                         | CONTROL | FILTRATE | VACCINE |
|-------------------------|---------|----------|---------|
| RABBITS AFFECTED        | 81      | 66.7     | 70      |
| BOWEL LESION OBSTRUCTED |         | 5.5      |         |
| GALLBLAD                | 25      | 22.2     | 15      |
| "STONES"                | 6       |          |         |
| HEART                   | 6       | 5.5      | 5       |
| JOINTS                  | 25      | 22.2     | 6       |
| KIDNEYS                 | 6       | 11       | 5       |
| LIVER                   |         |          | 5       |
| LUNGS                   |         | 5.5      | 5       |
| SKIN ABSCESES           |         |          | 10      |
| STOMACH ULCERS          |         | 5        | 10      |
| TESTES ABSCESED         |         |          | 5       |
| STREP. ISOLATED FROM    |         |          |         |
| BILE                    | 6       | 5.5      | 10      |
| JOINTS                  | 6       | 5.5      | 5       |
| KIDNEYS                 |         | 5.5      |         |
| LIVER                   |         |          | 5       |

*Studies on Immunity against the Streptococcus  
Antigen 7 S. non-hemolytic (5004)  
9/5/24 2/1/25*

Fig. 2

dressings. Six—with the filtrate. We succeeded in producing almost complete immunity only with the filtrate.

During the last three years gradually we segregated the cultures of streptococci which were capable of producing visceral infection. At no time during the eight years were we able to produce or to obtain a strain which consistently produced a peptic ulcer although we were able to obtain peptic ulcer with several different varieties of streptococci. The gall bladder, on the other hand, showed a far greater frequency in its response to these organisms. The most successful organism that we used to produce chronic cholecystitis was a non-hemolytic streptococcus from a stool of a patient with colitis but we were able to produce chronic cholecystitis not only with the non-hemolytic group from the bowel but with the viridans affecting the teeth and with several hemolytic throat strains. In

staphylococcus albus as of importance from nasal cultures. Predominating hemolytic or viridans cultures from the throat in the presence of obvious infection may be of significance. Both the viridans and hemolytic from infected teeth are, in our experience, important. In duodenal study we attach little significance to this first specimen but a predominant organism after stimulation and found in the B. bile may be of great importance. This refers to the colon, streptococcus and staphylococcus groups. In our experience the bacteriology of the nose and throat and mouth and the organisms found in the throat are frequently encountered in the first specimen. We insist however that only a predominant organism after stimulation and associated with cystologic evidence of possible infection is of importance.

We would finally report a series of experiments which were destined to demonstrate whether or not it was possible to produce immunity against some of the streptococcal strains. It has been our desire from the beginning of this investigation to obtain an organism which would produce a visceral lesion with a relative degree of certainty. Two years ago we were able to obtain a non-hemolytic streptococcus from the stool which produced the greatest frequency of gall bladder lesions as well as joint changes. We then took a series of rabbits and we inoculated them both with the filtrate and with a vaccine containing 100 million organisms per cubic centimeter. We then carried out an immunization period which was 38 days in duration during which we inoculated with 2.6 c.c. of the filtrate or vaccine giving 10 doses in all. This was then followed by a 21 day rest period after which we divided into three groups. One—a control group which had received no immunization. Another, a filtrate group which had received the filtrate and finally, a vaccine group which received the vaccine. We then

inoculated simultaneously all three groups with a total 0.132 e.e. of a 24 hour broth culture of the organism in three doses. The entire series were then killed three months later and carefully studied. While it is only possible to briefly summarize the results of these studies which are clearly shown in Chart 3 it is to be noted that while 75% of the controls developed joint lesions the incidence was reduced to 6% by preventative inoculation, a figure which can be explained on no mere coincidence inasmuch as the animals selected were as nearly alike in weight as we could select. Less striking are the results seen with cholecystitis but even in this group it is apparent that the preventative inoculation group showed a smaller incidence of chronic visceral disease. Owing to the large amount of time and attention necessary to investigations of this type and the expense incurred it has not been possible for us to advance to the next problem which is one of paramount interest, that is, to reverse the procedure, producing disease first by inoculating a large series of animals and then subsequently treating them with the filtrate or vaccine. Our studies to date have had to do with preventative inoculation. The problem of the future is to determine the reverse, namely how far can we bring about cure by these bacterial procedures.

Our studies over the last eight years have emphasized the fact that it is not possible by ordinary means such as are available in routine bacteriological procedures to predict either the virulence of a chronic organism or its ability to strike a certain organ. This may be apparent during the acute stage of infection. It is far more difficult to demonstrate with chronic visceral disease but we do know that many carriers of foci of infection harbor organisms that are capable in laboratory animals of producing widespread visceral damage similar to that routinely encountered in ordinary gastro-enterological work. We are convinced that

### IMMUNITY STUDIES WITH STREPTOCOCCUS.

| ANIMAL | SERIES | GAST. | LEG. R. FORE | LEG. L. FORE | R. HIND | LEG. L. HIND | NUTRITION | CHOLECYST. | HEART | WINGS | LIVER | SPLEEN | JOINTS.                | KEY.              |
|--------|--------|-------|--------------|--------------|---------|--------------|-----------|------------|-------|-------|-------|--------|------------------------|-------------------|
| 123    | 123    | 0     | 0            | 0            | 0       | 0            | 2675      | 0          | 0     | 0     | 0     | 0      | SH + BRUSKING OF LIVER | AT + ATROPHY      |
| 124    | 124    | 0     | 0            | 0            | 0       | 0            | 2325      | 1470       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | ○ = CONTROL       |
| 125    | 125    | 0     | 0            | 0            | 0       | 0            | 2200      | 2200       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | CONT. CONTRACTED  |
| 127    | 127    | 0     | 0            | 0            | 0       | 0            | 2125      | 2100       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | ENDG. - CAPSITIS  |
| 128    | 128    | 0     | 0            | 0            | 0       | 0            | 2700      | 2700       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | HE + MEMBRANE     |
| 131    | 131    | 0     | 0            | 0            | 0       | 0            | 2325      | 2325       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | HEM. CAPSITIS     |
| 132    | 132    | 0     | 0            | 0            | 0       | 0            | 2225      | 2225       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | L. LAME DR. LIPS  |
| 133    | 133    | 0     | 0            | 0            | 0       | 0            | 2225      | 2225       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | M. POTTLED        |
| 134    | 134    | 0     | 0            | 0            | 0       | 0            | 2225      | 2225       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | MIT. MITRAL VALVE |
| 135    | 135    | 0     | 0            | 0            | 0       | 0            | 2225      | 2225       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | N. - NORMAL       |
| 136    | 136    | 0     | 0            | 0            | 0       | 0            | 2225      | 2225       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | O. - NEGATIVE     |
| 137    | 137    | 0     | 0            | 0            | 0       | 0            | 2375      | 2325       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | P. - PITTING      |
| 138    | 138    | 0     | 0            | 0            | 0       | 0            | 2450      | 2450       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | SC. - SCLEROSIS   |
| 139    | 139    | 0     | 0            | 0            | 0       | 0            | 2175      | 2175       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | SL. - SCLEROTIS   |
| 140    | 140    | 0     | 0            | 0            | 0       | 0            | 2550      | 2750       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | SUP. SUPPURATION  |
| 141    | 141    | 0     | 0            | 0            | 0       | 0            | 2650      | 2500       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | SW. - SWELLING    |
| 142    | 142    | 0     | 0            | 0            | 0       | 0            | 2250      | 2150       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | T. - TUMOR        |
| 143    | 143    | 0     | 0            | 0            | 0       | 0            | 2350      | 2350       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | TE. - TENDER      |
| 144    | 144    | 0     | 0            | 0            | 0       | 0            | 2700      | 2700       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   | - NO RECORDING    |
| 145    | 145    | 0     | 0            | 0            | 0       | 0            | 2125      | 2125       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 146    | 146    | 0     | 0            | 0            | 0       | 0            | 1475      | 1475       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 147    | 147    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 148    | 148    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 149    | 149    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 150    | 150    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 151    | 151    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 152    | 152    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 153    | 153    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 154    | 154    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 155    | 155    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 156    | 156    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 157    | 157    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 158    | 158    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 159    | 159    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 160    | 160    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 161    | 161    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 162    | 162    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 163    | 163    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 164    | 164    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 165    | 165    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 166    | 166    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 167    | 167    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 168    | 168    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 169    | 169    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 170    | 170    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 171    | 171    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 172    | 172    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 173    | 173    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 174    | 174    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 175    | 175    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 176    | 176    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 177    | 177    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 178    | 178    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 179    | 179    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 180    | 180    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 181    | 181    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 182    | 182    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 183    | 183    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 184    | 184    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 185    | 185    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 186    | 186    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 187    | 187    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 188    | 188    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 189    | 189    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 190    | 190    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 191    | 191    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 192    | 192    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 193    | 193    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 194    | 194    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 195    | 195    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 196    | 196    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 197    | 197    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 198    | 198    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 199    | 199    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |
| 200    | 200    | 0     | 0            | 0            | 0       | 0            | 2197      | 2197       | 0     | 0     | 0     | 0      | NO DEFINITE FINDINGS   |                   |

Fig. 3



the future will reveal methods for differentiating these virulent strains and probably combatting their pernicious influence on the digestive tract.

#### DISCUSSION:

DR. A. C. IVY (Chicago, Ill.): Several years ago, about this time and before this Association, I reported the difficulties that I and other workers in my laboratory have had in attempting to produce chronic ulcers of the stomach in rabbits and dogs by injecting bacteria that had been isolated from human ulcers.

We were able to obtain hemorrhagic erosions, ecchymotic hemorrhages and acute manifestations of that kind, but we were never able to obtain typical chronic ulcers. At that same time I stated that I had no reason, however, to disbelieve the claims of Rosenow, Hufford, and Nichols. I simply was unable to get their results.

Since Dr. Rehfuss is using rabbits, it may be of interest for me to report that if one sections the vagi just below the diaphragm in rabbits, and if they survive the operation longer than twenty days, 60 per cent of them will develop typically chronic, indurated ulcers. This is associated with gastric stasis; and the rabbit, you know, eats a very rough diet, oats, hay, and so forth.

Now, most bacterial filtrates, and I think whenever we inject bacterial suspensions of any kind, cause disturbances of the motility of the stomach and intestine. One observes spasms which may cause ecchymotic, petechial hemorrhages and erosions; and if the nutritional condition or the state of digestion of the animal is markedly altered, we might expect some of those acute lesions to become chronic. In the rabbit, I should like to point out again, we obtain typically chronic, indurated ulcers, by interfering with the motor activity of the stomach, namely, in the direction of production of stasis in the presence of mechanical trauma due to rough food.

In that regard I am tempted to say that I think most of our managements of peptic ulcer at the present time are palliative in nature only, and that we only get at the direct etiology, or only begin to bear upon the etiological factors, first, when we teach the patient how to live and how to eat; of course, if there are foci of infection, they should be cleared up for general reasons.

DR. ERNEST H. GAITHER (Baltimore): The Authors are to be congratulated upon this timely and important work.

The question of chronic visceral infection in relation to gastroenterological problems has been of outstanding interest to the profession for many years, and all internists are familiar with the researches of various investigators in regard to the specificity of bacterial invasion. However, it must be remembered that the thorough work of Swift appears to prove the lack of such specificity.

The theory that pathologic changes in the digestive tract may possibly have been inaugurated by septic emboli rather than by a single type of bacterium, has often been advanced, and for years we have pondered the question, considering in each and every case the relationship of infection to disease in this domain; some of the proof brought forward by these Authors causes us to realize that infection does in many instances fail to attack the digestive tract, and has a much greater affinity toward joints; again, when the digestive tract is invaded, the hepatobiliary system is more likely to be involved than the stomach or intestine.

The Authors make very notable observations regarding a strain of colon bacillus from a removed gall bladder, which they designate as "strain A," and its excessive toxicity as compared with the other strains, its continued toxicity after months of continual passage through rabbits, and the sudden hemorrhage and even perforation of the stomach produced by a lethal dose. After a sublethal dose, the organisms were usually found in either the biliary

or the urinary tract. Septicemia was caused by a larger dose, while smaller doses caused localization in the biliary tract, liver, and kidneys. Injection of the mesenteric system had similar results, and when these organisms were injected into the gall bladder, they were invariably found localized in the duodenum, while all cultures of the surrounding liver tissues were entirely negative. Because of the labile character of the digestive tract in rabbits and other animals, conservatism is advisable when application of the evaluated results to the human digestive tract is under consideration.

Here we may recall a fine piece of work by Braithwaite, who by a series of investigations called attention to the flow of lymph from the ileocecal angle, and its possible bearing on the cause of duodenal and gastric ulcer, suggesting that infection could reach that area by way of the lymph channels. In speaking of the action of infected lymph in producing gastroduodenal ulceration, he propounds the question: "Why then should the effects of the poisoned lymph be permanent only on the lesser curvature and near the pylorus?" and he answers by the statement: "It is in this place that lymph follicles are twice as numerous as, and are bigger than, those in any other portion of the stomach."

Wilkie suggested that emboli from thrombosed vessels in an infected omentum pass to the stomach and duodenum and give rise to ulceration.

Letulle claims to have produced gastric ulcer by inoculation of the general peritoneal cavity by the staphylococcus pyogenes aureus, probably via the great omentum.

Bolton and Balfour call attention to the fact that relics of a bacterial infection are to be found in the crater of many gastric ulcers.

Jaksch stated many years ago, that acute ulcers are known to occur in many infective diseases, e.g., puerperal fever, peritonitis, pleurisy, tuberculosis.

After careful perusal of the present paper one is immediately convinced of the comprehensiveness of the study and the difficulty of applying dependable tests and correctly interpreting the results. One of the most interesting points was the Authors' ability to produce by very small, graduated doses, an immunity sufficient to withstand the lethal dose of the organism in its most virulent form, causing a total disappearance of the organism in practically every organ of the body. They make an enlightening statement in regard to the large number of individuals who respond with a positive skin reaction to colon antigens, and the frequency with which certain individuals show a marked skin reaction to certain strains in contrast with others, and they naturally stress the importance of investigating this peculiar tendency of the digestive invalid to respond differently to colon strains. In this connection they demonstrated that the colon vaccine from one organ would produce reactions in a different organ or groups of organs.

Their studies of the action of streptococci upon the digestive tract are interesting and call for further study; time will not permit us to discuss this phase of their investigations except to say that the vast majority of lesions produced were found in the joints, heart and kidneys; also that at no time during the eight years of investigation were they able to produce or obtain a strain which consistently produced a peptic ulcer. The gall bladder showed a far greater frequency in its response to these organisms, and in the majority of instances they were able to recover the organisms from the gall bladder wall. It is well to ponder this observation in regard to the views of those who claim that drainage of the gall bladder relieves or cures disease of a part or the whole of the biliary tract. They emphasize that these studies embracing 1300 animals proved arthritis to be the commonest lesions encountered.

To me, one of their most interesting and instructive notations was that cultures from gastric ulcer at operation, revealing the viridans streptococcus, failed to produce

experimental ulcer. Certainly these observations do not bear out the assertions of those who have proclaimed specificity of bacterial invasion, having particularly to do with the digestive tract. It is well to take cognizance of their definite assertion that the bacteriology of the bile is largely dominated by the bacteriology of the nose, throat, and mouth, and that organisms found in the throat are frequently encountered in the first specimen. They insist, however, that "only a predominant organism after stimulation and associated with cytologic evidence of possible infection is of importance."

They report a series of experiments destined to demonstrate whether or not it was possible to produce immunity against some of the streptococcal strains, and their successful results in those with joint and gall bladder lesions were quite striking; those in the latter group less so than in the former, however.

Because of the fact that these investigators have not completed their interesting and important research, and are not as yet ready to present definite conclusions, it is impossible to do more than point out the great value of their work, and to lend our encouragement, so that they and their confreres may continue this meritorious line of endeavor.

DR. MARTIN E. REHFUSS (in closing the discussion): Dr. Guither helped me out because he read part of the paper. You will have to read the paper to get the details regarding this subject. I know there was so little time at my disposal I would have to hurry.

As to the question of immunity, so far as that was concerned we tried several methods of immunizing against colon bacillus. We failed absolutely.

(Slide) Means of using the living organism.

(Slide) These are a few slides to show attempted immunization in animals.

(Slide) But, unfortunately, in none of them did we succeed until we used living organism in the rabbits, which I wouldn't dare do with a human being, but with the living organism we were able to produce immunity. After this we gave a "lethal dose," which didn't kill the animal, and twenty-four hours afterward we sacrificed these animals and not a single colon bacillus was found in the organs.

(Slide) Here is an interesting series on joints. We got strains that produced joints right along. Here is one using six different methods of immunity: subcutaneous, autoclave, subcutaneous living, intradermal living, intradermal autoclaved cultures, Besredka skin, and Berkfeld filtrate methods. Every one of the animals in this group except this one (indicating), the filtrate developed arthritis. That was a streptococcus obtained from the cervical smear.

(Slide) This is the interesting one in which we finally got an organism which produced arthritis in 80 per cent of the cases. We injected one hundred animals and obtained pathologic joints in the overwhelming majority, and did it in the following way: This is based on trend of weight graphs during the respective periods, immunization over thirty-eight days in duration, and consisted in inoculation of both the filtrate and the vaccine. This would hit the joints in about 80 per cent of the rabbits and it was a non-hemolytic type organism which came from the bowel. We then had the control group.

(Slide) Here is the result after three and a half months, or nearly four months, and the most striking thing is 75 per cent of the controls had joint disturbances. (We have photographs and motion pictures) while the vaccinated animals showed only 6 per cent, which I should say was fairly successful vaccination.

So far as the other organs were concerned, it wasn't so successful. With the non hemolytic streptococcus, which was the most successful one in striking the gall bladder, 25 per cent produced gall bladder disease, and in the vaccinated group only 15 per cent.

It took us a whole summer to produce this chart, but we are satisfied that this joint disturbance can come not only from the nose and the throat organisms but also from the intestinal tract. The organism most successful in producing arthritis, was a colon organism and a non hemolytic streptococcus. People don't pay much attention to the colon in arthritis, but to teeth and tonsils, but I think in arthritis intestinal disease should receive more attention on our part and that might clear up some of these cases.

This is the most interesting chart we have because it proves beyond reasonable doubt, to my mind, that with that strain we were able to reduce the incidence of arthritis, at least from 75 per cent to 6 per cent.

## ABSTRACTS

LEE, W. E., M.D., F.A.C.S., AND TAYLOR, J. S., M.D.  
*"Argentaffin Tumors of the Terminal Ileum." A Cause of Intestinal Obstruction. S. G. and O., Vol. 59, No. 3, Sept., 1934.*

In this article, the Authors report two very interesting cases of argentaffin tumors of the terminal ileum, which were causing intestinal obstruction and which well might be mistaken for carcinomata.

The Authors review the work of Mnson, who discovered the silver reducing properties of the cytoplasmic granules in the tumor cells of these carcinoids. He has shown that these tumors begin with the migration of the Nicholas-Kulchitzky cells in the intestinal mucosa into the neuro-mata in the wall of the intestines. These cells then grow very slowly, but eventually break through the nerve filament and invade the surrounding tissue. Metastases are rare, but the primary growth often may obstruct the intestinal lumen and occasional metastases to the regional lymph nodes are found.

Two cases are reported in detail. In both, small tumors at the terminal ileum were found and following radical removal these patients have been well for twenty-two and twenty-three months respectively.

Argentaffin tumors resemble carcinomata in that they

invade tissues locally and extend into the regional lymph nodes. They may be differentiated from the usual carcinomata by their yellow color, firm consistency, the absence of necrosis, lack of mitosis in the tumor cells and the ability of the cytoplasmic granules to reduce silver salts. The cases are usually of long duration before the terminal stages of cachexia.

N. W. Swinton, Boston.

WILLIAM BOYD.

*The Relationship of Polycythemia to Duodenal Ulcer. Winnipeg, Canada, p. 589-594, Vol. 187, May, 1934.*

The association of duodenal and gastric ulcer with polycythemia has been previously reported by other Authors. The relationship, if any, between the two conditions has seemed difficult if not impossible to determine. Boyd presents this case of the association in a patient of polycythemia, leukocytosis, splenomegaly, duodenal ulcers, myocardial fibrosis, coronary artery occlusion and marked ascites. The question whether the increased red cell count should be regarded as a true polycythemia or as a secondary erythrocytosis is discussed with a final conclusion that in this case the polycythemia is primary and probably bears a causal relationship to the duodenal ulceration.

M. E. Gabor, Milwaukee.

## SECTION II—*Experimental Physiology*

### The Cause of the Faulty Digestion in Dogs Without Stomachs

By

EDWARD S. EMERY, Jr., M.D.\*  
BOSTON, MASSACHUSETTS

#### INTRODUCTION

THE writer's interest in the effect of gastrectomy on digestion goes back to 1928. In this year one of his patients developed large bulky stools with a high content of fat following the removal of approximately two-thirds of the stomach for an extensive carcinoma. The possibility of metastases in the pancreas naturally occurred to him, but there was no other evidence to confirm this suspicion. X-ray studies were entirely negative. The stools did not have the gross appearance and did not contain the quantity of starch with which we associate disease of the pancreas. A study of the literature brought to his attention the article of Gabrila and Danicico (1), in which those Authors showed that an increased elimination of fat followed resection of the stomach. As this was new to him and there was so little in the literature about the effect on digestion of removing the stomach, he decided to study the problem on dogs, particularly to determine why the removal of the stomach caused a greater loss of fat *via* the stools.

#### LITERATURE

In 1878 Czerny and Kaiser (2) reported that they had successfully performed a total gastrectomy on a dog. However, an autopsy after five years of life revealed that a small remnant of the stomach had been left and had formed a pouch. Hence the credit for the first true total gastrectomy seems to go to Carvallo and Pachon (3). These workers reported the removal of a dog's stomach in 1894.

The first total gastrectomy was done on man in 1883 by the American surgeon Connor (4), but the patient died on the table. It was 14 years later, in 1897, that a successful total gastrectomy on man was reported by Carl Schlatter (5), an assistant of Krönlein at Zurich.

Few of these operations were performed in ensuing years because of the technical difficulties and the seemingly little use for the operation. However, the growing recognition that former methods of treating peptic ulcer leave much to be desired, stimulated the surgeons to remove greater amounts of the stomach. The greater success experienced with these operations has en-

couraged more radical surgery with the result that operations for total gastrectomy are reported not infrequently. Stahnke (6) counted 62 successful gastrectomies in 1933 and by 1934 Ducuing *et al* (7) were able to list 132. As the latter writers point out, this does not tell how many unreported gastrectomies have been performed.

Within recent years, therefore, the effect of gastrectomy on the bodily processes has become a practical question. Previously to this time it has been the physiologists who have been interested primarily in this subject, and it is interesting perhaps to observe that most writers in recent years have paid more attention to the effect of gastrectomy on the blood than on the digestion.

Physiologists have made numerous studies in the past on the effect of removing various portions of the intestinal tract. For the most part their observations have dealt with resections of the small intestine, probably because this seemed to have a more practical bearing on human problems. It does not seem worth while to review all this work. In general, the results have shown that removal of sufficient portions of the gastro-intestinal tract results in an obvious loss of fat as revealed in the stools. The loss of nitrogen has not been so great. Most observers have agreed that an increased loss of fat, which follows a greater intake, is accompanied by an increased loss of nitrogen. Less attention has been given to the effect, which partial removal of the intestines produces on the assimilation of carbohydrates. Those who have studied this phase of the problem conclude that there is relatively little if any effect on their digestion. One may question the results regarding carbohydrates with justification, because the methods of studying them are rather unsatisfactory.

Few studies have been made on the digestion of man after the stomach has been removed in whole or in part. Moreover, the findings have been conflicting, and there has been no unanimity of opinion concerning the cause of the abnormalities in digestion when they have been encountered.

Hofmann (8) found that the amount of nitrogen in the stools of Schlatter's patient was normal when the individual was on a bread and milk diet. Heilmann (9) found a lowered assimilation of fat in three patients. There was a normal digestion of nitrogen in one patient, whereas there was an increased output of nitrogen in the stools of the third case. Troell,

\*Associate in Medicine, Peter Bent Brigham Hospital, with the Technical Assistance of Miss Eleanor P. Hicken.  
Read at the 38th Annual Session of the American Gastro-Enterological Association, Atlantic City, N. J., June 10-11, 1935.  
Approved by the Publications' Committee of the Association.  
†The expenses for this study were defrayed by The Proctor Fund for the study of chronic disease.

Losell and Karlmark (10) report a normal digestion in their patient.

Soloviev (11) studied only the nitrogen and concludes, from one patient, that removal of the stomach does not increase the loss of nitrogen. Shima (12) found that total extirpation of the stomach resulted in a disturbance of the fat metabolism, but that the protein metabolism was disturbed in only one of the three patients.

Gabrila and Danicio (1), from their study of 13 patients upon whom gastro-enterostomies and various kinds of subtotal gastrectomy had been performed, report that the digestion of fats was impaired in all the patients, whereas the digestion of protein was impaired only in 8. These Authors believe that the failure of digestion is the result of a pancreatic insufficiency following resection of the stomach. They believe that hepatic insufficiency must play a rôle also because occasionally the digestion of proteins is normal and the digestion of fats is much impaired. They believe also that an increased motility may be responsible for the digestive deficit because in nearly all cases of resection of the stomach the passage of food is greatly accelerated—ingested powdered charcoal appearing in the stools after 12 hours.

Burger and Konjetzny (13) found a disturbance in the digestion of nitrogenous foods after a large proportion of fat had been given in the diet; they believe the loss of nitrogen is caused by a laxative action of the fats.

Those observers who report abnormal digestion give different explanations for their findings. Burger and Konjetzny suggest that the anomaly is due to a lack of secretion of the intestinal glands dependent upon an absence of hydrochloric acid. Ducuing believes that there is a deficient pancreatic secretion probably as a result of achlorhydria.

This would seem to explain the situation in the cases reported by Von Haberer (14) and Drevermann (15) in which a diarrhea was controlled by giving an acid-pepsin mixture.

Gabrila and Danicio consider that their findings were the result of a disturbance in motility and an insufficiency of the pancreatic and biliary secretions. It is interesting that the case of Troell *et al.*, in which no abnormality of digestion was found, had a normal motility. Heilmann, on the contrary, found that the rate of motility was 18 hours and that a hyperistalsis was present in the whole digestive tube. He found the colon filled in 2½ hours. Schwartz (16) reported a motility rate of 19 hours as opposed to 36 hours in the case reported by Dreverman.

A summary of the literature reveals that no constant changes occur after extirpation of the stomach. Digestion may be normal or markedly deficient. Furthermore, there is no relationship between the behavior of the nitrogen and fats. The literature seems to suggest, however, that there is a greater tendency toward a disturbance in the digestion of fat than that of nitrogen. The assimilation of nitrogen has been normal in several patients, although the digestion of fat was abnormal, whereas the reverse is less likely to occur.

#### METHODS OF STUDY

The method of investigation was devised to determine the proportion of food substances lost through the feces of dogs after a total gastrectomy had been done.

Weighed diets were given and the food analyzed for its content of nitrogen, fat and ash according to the method outlined by McCrudden (17). The amount of carbohydrate was determined by subtraction. Usually the diet was given for five days before the collection of stools was started, but, in a few instances, this period of time was decreased to three days. Carmine was used at the beginning and at the end of the test-period to delimit the stools. Unless otherwise indicated, the period of stool collection was three days.

After the stools had been collected, their gross appearance was noted and their weight obtained. They were then acidified with dilute hydrochloric acid and dried at a temperature of 105° C. After drying, they were again weighed, ground and placed in tightly stoppered bottles.

The nitrogenous content was determined in the usual way by the Kjeldahl method. The fats were determined by the method of Folin and Wentworth (18). These Authors believe their procedure gives somewhat higher values for fat than the methods previously in use. They state that soaps cannot be entirely freed from fatty acids and that the attempt to do so leads to such inaccurate results as to make the procedure of little value. Therefore, we determined only the total fats, fatty acids and neutral fats. Since no significant differences occurred in the fatty fractions, the results are reported only in terms of the total fat. The ash was determined in the usual way by incinerating in a quartz crucible.

The determination of the carbohydrates was found to be most unsatisfactory. We first used Bertrand's procedure and later a yeast method suggested to us by Dr. Trimble. But the results were quite inconstant, and the total quantity which was obtained by this method was much less than by the process of subtraction. This difference was too marked to be explained by a reasonable error in the method. Because the stools could not be collected immediately after defecation, the opportunity for bacterial destruction made it impossible to obtain accurate results. Therefore, the carbohydrates were eliminated from this study.

Control studies were made on 16 normal dogs, and two animals were studied whose stomachs were shown at autopsy to have been completely removed. The stomachs of these dogs had been removed two years before for Dr. William P. Murphy who had been observing their blood. He kindly gave them to us. They were in good health and showed no evidence of anemia at any time.

Dog 4 was sacrificed and autopsied at the end of 1½ years, having lived for 3½ years in good health. Dog 5 was sacrificed after we had studied him for 3 years, he having continued in fair health for 5 years. The use of animals who had been without stomachs for 2 years was of value in this study because any abnormal digestion was of a permanent nature and ruled out the possibility of a temporary change following operations.

After determining that the animals without stomachs showed faulty digestion, the following plan was used to investigate the cause. Absence of the stomach might influence digestion by any one of the following ways: (1) loss of the digestive function of the stomach, (2) decreased or absent production of the secretions of the duodenum, pancreas and gall bladder, (3) increased motility.

Ludwig and Ogata (19) and Schmidt and Strassburger (20) have shown that in the absence of pepsin and hydrochloric acid the only evidence for failure of digestion occurs in raw connective tissue. No studies have been made on the importance or otherwise of the emulsification of fats in the stomach. Therefore, we studied this point.

We studied also the effect of supplying hydrochloric acid and made one observation on the effect of feeding each one of the following substances: fresh pancreas and pancreatin plus bile. Finally, we studied the motility of the

gastro-intestinal tract by indicators, by the X-ray and by small feedings.

### ILLUSTRATIVE PROTOCOLS METABOLISM DETERMINATION 3: DIGESTION OF NORMAL DOG

*Dog No. 3.*—Normal adult female. Weight 13 kilos.

November 19, 1930. Dog started on diet of 350 grams of boiled horse meat and 100 grams of bread per day.

November 24. Carmine given to mark beginning of test period.

November 27. Carmine given to mark end of test period. Stools collected including both earmines.

Food:

|                      |             |               |
|----------------------|-------------|---------------|
| Nitrogen:            | 50.88 grams |               |
| Fats:                | 27.6 grams  | Dry weight:   |
| Feces: Moist weight: | 135.0 grams | 49.0 grams    |
| Nitrogen:            | 3.56 grams  | 7.28 per cent |
| Fats:                | 1.34 grams  | 2.73 per cent |
| Nitrogen absorbed:   | 47.32 grams | 93.0 per cent |
| Fat absorbed:        | 26.26 grams | 95.0 per cent |

### METABOLISM DETERMINATION 39: DIGESTION OF LARGE AMOUNT OF FAT

*Dog No. 2.*—Normal virgin female. Weight 13.3 kilos.

September 7, 1931. Dog started on diet of 350 grams of boiled horse meat, 100 grams of bread and 200 grams of lard per day.

September 11, 1931. Carmine given to mark beginning of test diet.

September 16, 1931. Carmine given to mark end of test diet. Stools collected including both carmines.

Food:

|                      |              |                |
|----------------------|--------------|----------------|
| Nitrogen:            | 76.3 grams   |                |
| Fat:                 | 1241. grams  | Dry weight:    |
| Feces: Moist weight: | 193. grams   | 64 grams       |
| Nitrogen:            | 3.81 grams   | 5.96 per cent  |
| Fat:                 | 3.87 grams   | 6.04 per cent  |
| Nitrogen absorbed:   | 72.51 grams  | 95.00 per cent |
| Fat absorbed:        | 1237.6 grams | 99.00 per cent |

### METABOLISM DETERMINATION 3: DIGESTION IN ABSENCE OF STOMACH

*Dog No. 4.*—Adult male with stomach removed in 1928. Weight 12.9 kilos.

November 19, 1930. Dog started on diet of 350 grams of boiled horse meat and 100 grams of bread.

November 24. Carmine given to mark beginning of test period.

November 27. Carmine given to mark end of test period. Stools collected including both earmines.

Food:

|                      |             |                |
|----------------------|-------------|----------------|
| Nitrogen:            | 50.88 grams |                |
| Fat:                 | 27.6 grams  | Dry weight:    |
| Feces: Moist weight: | 691. grams  | 169 grams      |
| Nitrogen:            | 15.36 grams | 9.09 per cent  |
| Fat:                 | 21.59 grams | 12.78 per cent |
| Nitrogen absorbed:   | 35.52 grams | 70.00 per cent |
| Fat absorbed:        | 6.01 grams  | 22.00 per cent |

### METABOLISM DETERMINATION 4: DIGESTION IN ABSENCE OF STOMACH

*Dog No. 5.*—Male Shepherd. Total gastrectomy done in 1928. Weight 12.8 kilos.

November 19, 1930. Dog started on diet containing 350 grams of boiled horse meat and 100 grams of bread per day.

November 24. Carmine given to mark beginning of test period.

November 27. Carmine given to mark end of test period. Stools collected including both earmines.

Food:

|                      |             |                |
|----------------------|-------------|----------------|
| Nitrogen:            | 50.88 grams |                |
| Fat:                 | 27.6 grams  | Dry weight:    |
| Feces: Moist weight: | 585.0 grams | 166 grams      |
| Nitrogen:            | 14.54 grams | 8.76 per cent  |
| Fat:                 | 23.02 grams | 13.87 per cent |
| Nitrogen absorbed:   | 36.34 grams | 72 per cent    |
| Fat absorbed:        | 4.58 grams  | 17 per cent    |

### METABOLISM DETERMINATION 11: DIGESTION OF EMULSIFIED FAT

*Dog No. 4.*

December 12, 1930. Diet started of 350 grams of boiled horse meat, 100 grams of bread, and 250 grams of medium grade cream.

December 17. Carmine given to mark beginning of test period.

December 20. Carmine given to mark end of test period. Stools collected including both earmines.

Food:

|                      |              |                |
|----------------------|--------------|----------------|
| Nitrogen:            | 120.9 grams  |                |
| Fat:                 | 228. grams   | Dry weight:    |
| Feces: Moist weight: | 427 grams    | 259 grams      |
| Nitrogen:            | 18 grams     | 6.95 per cent  |
| Fat:                 | 147.4 grams  | 56.92 per cent |
| Nitrogen absorbed:   | 102.88 grams | 85. per cent   |
| Fat absorbed:        | 80.20 grams  | 35. per cent   |

### METABOLISM DETERMINATION 10: DIGESTION OF EMULSIFIED FAT

*Dog No. 5.*

December 12, 1930. Diet started of 350 grams of boiled horse meat, 100 grams of bread and 250 grams of medium grade cream per day.

December 17. Carmine given to mark beginning of test period.

December 20. Carmine given to mark end of test period. Stools collected including both carmines.

Food:

|                      |             |                |
|----------------------|-------------|----------------|
| Nitrogen:            | 120.9 grams |                |
| Fat:                 | 228. grams  | Dry weight:    |
| Feces: Moist weight: | 1015 grams  | 352 grams      |
| Nitrogen:            | 29.67 grams | 8.43 per cent  |
| Fat:                 | 113.6 grams | 32.28 per cent |
| Nitrogen absorbed:   | 91.2 grams  | 75. per cent   |
| Fat absorbed:        | 114.0 grams | 51. per cent   |

### METABOLISM DETERMINATION 16: EFFECT OF TENTH NORMAL HYDROCHLORIC ACID

*Dog. No. 5.*

February 12, 1931. Diet started consisting of 350 grams of boiled horse meat, 100 grams of bread, 50 grams of lard and 500 c.c. of tenth normal hydrochloric acid per day.

February 17. Carmine given to mark beginning of test period.

February 19. Carmine given to mark end of test period. All stools collected including both earmines.

Food:

|                      |              |                |
|----------------------|--------------|----------------|
| Nitrogen:            | 38.2 grams   |                |
| Fat:                 | 171. grams   | Dry weight:    |
| Feces: Moist weight: | 478 grams    | 154 grams      |
| Nitrogen:            | 8.42 grams   | 5.47 per cent  |
| Fat:                 | 52.33 grams  | 33.98 per cent |
| Nitrogen absorbed:   | 29.74 grams  | 78 per cent    |
| Fat absorbed:        | 118.37 grams | 69 per cent    |

### METABOLISM DETERMINATION 40: EFFECT OF FRESH PANCREAS

*Dog No. 5.*

September 21, 1931. Started diet consisting of 350 grams of boiled horse meat, 100 grams of bread and 450 grams of fresh pancreas per day.

September 22. Carmine given to mark beginning of test period.

September 24. Carmine given to mark end of test period. Stools collected including both carmines.

|        |                    |              |                |
|--------|--------------------|--------------|----------------|
| Food:  | Nitrogen:          | 60.42 grams  |                |
|        | Fat:               | 140.74 grams | Dry weight:    |
| Feces: | Moist weight:      | 784 grams    | 173 grams      |
|        | Nitrogen:          | 3.56 grams   | 2.06 per cent  |
|        | Fat:               | 71.29 grams  | 41.21 per cent |
|        | Nitrogen absorbed: | 56.86 grams  | 94 per cent    |
|        | Fat absorbed:      | 69.45 grams  | 49 per cent    |

#### METABOLISM DETERMINATION 52: EFFECT OF PANCREATIN AND BILE

*Dog No. 5.*

December 20, 1931. Started diet consisting of 350 grams of boiled horse meat, 100 grams of bread and 50 grams of lard mixed with 1 gram of pancreatin and 8 grams of powdered bile which had been incubated at 37.5 C. for 6 hours.

December 23. Carmine given to mark beginning of test period.

December 25. Carmine given to mark end of test period. Stools collected including both carmines.

|        |                    |              |                |
|--------|--------------------|--------------|----------------|
| Food:  | Nitrogen:          | 38.16 grams  |                |
|        | Fat:               | 170.7 grams  | Dry weight:    |
| Feces: | Moist weight:      | 267 grams    | 98 grams       |
|        | Nitrogen:          | 6.33 grams   | 6.46 per cent  |
|        | Fat:               | 18.31 grams  | 18.69 per cent |
|        | Nitrogen absorbed: | 31.83 grams  | 83.0 per cent  |
|        | Fat absorbed:      | 152.39 grams | 89.0 per cent  |

#### METABOLISM DETERMINATION 55: THE ABSORPTION OF FATTY ACIDS

*Dog No. 5.*

January 12, 1932. Started diet consisting of 350 grams of boiled horse meat, 100 grams of bread and 39 grams of fatty acids derived from lard and 2.02 grams of glycerine.

January 12. Carmine given to mark beginning of test period.

January 15. Carmine given to mark end of test period. Stools collected including both carmines.

|        |                    |              |                |
|--------|--------------------|--------------|----------------|
| Food:  | Nitrogen:          | 51.2 grams   |                |
|        | Fat:               | 190.0 grams  | Dry weight:    |
| Feces: | Moist weight:      | 528 grams    | 179 grams      |
|        | Nitrogen:          | 8.44 grams   | 4.72 per cent  |
|        | Fat:               | 49.35 grams  | 27.57 per cent |
|        | Nitrogen absorbed: | 42.44 grams  | 84 per cent    |
|        | Fat absorbed:      | 141.25 grams | 74 per cent    |

#### METABOLISM DETERMINATION 58: EFFECT OF SLOW FEEDING

*Dog No. 5.*

March 23, 1932. Diet started consisting of 75 grams of boiled horse meat, 50 grams of bread, and 50 grams of lard. Dog was fed so that approximately 8 grams of fat entered the intestine every half hour. This was carried out for 2 days.

March 23. Carmine given to mark beginning of test period.

March 24. Carmine given to mark end of test period. All stools collected including both carmines.

|        |                    |             |                |
|--------|--------------------|-------------|----------------|
| Food:  | Nitrogen:          | 7.25 grams  |                |
|        | Fat:               | 101.9 grams | Dry weight:    |
| Feces: | Moist weight:      | 126 grams   | 57.0 grams     |
|        | Nitrogen:          | 6.77 grams  | 11.89 per cent |
|        | Fat:               | 2.38 grams  | 4.17 per cent  |
|        | Nitrogen absorbed: | 6.48 grams  | 7.0 per cent   |
|        | Fat absorbed:      | 99.52 grams | 98.0 per cent  |

#### PROTOCOL ROENTGENOGRAPHIC OBSERVATIONS ON MOTILITY

*Experiment 1.—Normal dog.*

Feb. 2, 1931. Animal given 100 grams of meat, 50 grams of bread and 50 grams of barium.

1½ hours p.e. Barium scattered in small intestine.

4 hours p.e. Stomach seven-eighths empty. Barium had reached cecum.

6½ hours p.e. Barium to splenic flexure and in descending colon. Jejunum empty.

*Experiment 2.—Normal dog.*

Feb. 8, 1931. Animal given 100 grams of meat, 50 grams of bread and 50 grams of barium.

1½ hours p.e. Barium scattered thinly in small intestine.

3½ hours p.e. Stomach half empty. Barium in jejunum and ileum.

6½ hours p.e. Stomach empty. Colon filled to splenic flexure.

*Experiment 3.—Normal dog.*

Feb. 13, 1931. Animal given 100 grams of meat, 50 grams of bread and 50 grams of barium.

3½ hours p.e. Stomach half filled. Small intestine well filled.

4½ hours p.e. Stomach almost empty. Lower ileum well filled.

6 hours p.e. Stomach empty. Colon ¾ filled—only small amount left in ileum.

*Experiment 4.—Dog 5. Pathological.*

Feb. 2, 1931. Animal given 100 grams of meat, 50 grams of bread and 50 grams of barium.

4½ hours p.e. Upper intestine markedly dilated, lower somewhat.

6½ hours p.e. Some in duodenal pouch. Colon filled and dilated. Ileum empty.

*Experiment 5.—Dog 5. Pathological.*

Feb. 8, 1931. Animal given 100 grams of meat, 50 grams of bread and 50 grams of barium.

¼ hour p.e. Upper intestine well filled, dilated. Barium well along jejunum.

1½ hours p.e. Intestine well filled throughout.

3¾ hours p.e. Barium appears to be near cecum.

5¾ hours p.e. Colon still empty.

*Experiment 6.—Dog 5. Pathological.*

Feb. 13, 1931. Animal given 100 grams of meat, 50 grams of bread and 50 grams of barium.

3¾ hours p.e. Both jejunum and ileum filled.

4 hours p.e. No apparent change.

6 hours p.e. Barium in colon.

6½ hours p.e. Barium has reached rectum but plenty of material in small intestine.

#### PRESENTATION OF RESULTS

Twenty-nine studies were made on 6 normal dogs to obtain results which could serve as controls. Animals were chosen whose size (approximately thirteen kilograms) were similar to that of the dogs without stomachs.

The absorption of nitrogen and fat was high in every study but one. Variations occurred as follows: The per cent of nitrogen absorbed varied from 86.0 to 98.0 except on one occasion when it was 68.0. The absorption of fat varied from 87 to 99 per cent. The high figures were due to the way by which the stools had to be collected, which resulted in the loss of some fecal material. However, since the same method was used for the collection of the stools from the dogs without stomachs, any differences in absorption would be recognizable.

The normal animals were able to absorb large quantities as well as small quantities of fat. Seven to 257 grams of fat were fed per day, and the per cent of



fat which was absorbed was as high with the larger amount as with the smaller.

In contrast to these findings the 2 dogs without stomachs showed a definitely lower ratio between the amount of nitrogen and fat in the stools to the amount fed. Expressed in terms of absorption, the nitrogen varied from 64 to 88 per cent. The absorption of fat was smaller and varied from 17 per cent to 86 per cent. The average absorption of nitrogen and fat in 16 studies made on the two dogs without stomachs was 76 per cent and 59 per cent respectively. The average absorption of nitrogen and fat by the normal dogs was 92 per cent and 97 per cent respectively. Hence the dogs without stomachs absorbed on the average 16 per cent less nitrogen and 38 per cent less fat.

### STUDIES OF THE STOOLS

A consideration of the stools may be of some interest. Those from the pathological dogs were softer and of a different color. They were never formed but could be described as "mushy" in consistency in nearly all instances. On only one or two occasions were they so soft as to be liquid. They never had the dark brown or black color characteristic of the normal stool of a dog. Instead, they were a light gray and showed some soft mucus intimately mixed with the stool.

Gross evidences of fat were apparent in some specimens, thus providing the qualities of greasiness and a sheen. Table 1 compares the main characteristics

TABLE I

*A Comparison of the Stools from the Normal and Pathological Dogs*

|                                         | Normal | Pathological | Difference |
|-----------------------------------------|--------|--------------|------------|
| 1. Weight per day in grams.             | 21.5   | 50.6         | 29.1       |
| 2. Per cent of water in stools.         | 56.5   | 67.2         | 10.7       |
| 3. Weight of fat per day in grams.      | 1.39   | 14.04        | 12.65      |
| 4. Weight of nitrogen per day in grams. | 0.86   | 3.65         | 2.79       |

of the stools from the normal and the pathological dogs.

There seems to be no question, therefore, that absence of the stomach may result in an abnormal elimination of fat and nitrogen and may be accompanied by the passage of stools which are looser and softer than normal.

### STUDIES ON THE CAUSE OF MALABSORPTION

Since the first process in the digestion of fats is thought to be emulsification, it seemed advisable to determine whether there would be any difference in

the utilization of an emulsified fat, as cream, over that of lard. Dogs numbered 4 and 5 were tested with a diet in which the bulk of the fat was given in the form of 20 per cent cream. However, there was no better utilization of cream than of lard. (See metabolism determinations, No. 11 and No. 10).

The next idea that occurred to us was that the absence of hydrochloric acid might be the important element, particularly because of the gross appearances of the stools. These were not unlike the type of stool which is encountered with patients who have complete achlorhydria and are relieved by the administration of hydrochloric acid.

Therefore, Dog No. 5 was started on increasing amounts of tenth normal hydrochloric acid. By the end of ten days the animal was taking 500 c.c. of acid solution with his diet without any great evidence of distaste for it. Grossly, the stools appeared more normal. Both the color and consistency had improved. There was, in fact, a slight decrease in the water content of the stool (see Table 2). The amount of fecal material, as determined by weight, was less when the dogs were taking acid than when they were not.

There was also some evidence that digestion was slightly better when acid was given. In six observations made on Dog No. 5, from 67 to 88, with an average of 78 per cent of the nitrogen in the diet was utilized, or 2 per cent better than without acid. From 45 to 90, with an average of 73, per cent of the fat was absorbed which was 14.0 per cent more than when no acid was given.

Next we tried the effect of giving some of the digestive enzymes in the form of freshly chopped pancreas and pancreatin plus desiccated bile.

When 450 grams of fresh pancreas was fed with the diet, 94.0 per cent of the ingested nitrogen was absorbed and 49.0 per cent of the fat. (See metabolism determination 40).

The attempt to add bile to the diet met with failure. Fresh bile was procured from the slaughter house and was given to the animal in quantities of 500 c.c. mixed with the diet. Diarrhea followed promptly the ingestion of so much bile, and this was true of 200 c.c. of bile. Since the administration of lesser amounts would seem to be futile as a therapeutic procedure, we did not persist in the attempt.

Later, however, one observation was made on the effect of mixing 8 grams of powdered bile and 1 gram of pancreatin with the diet and incubating for 6 hours at 37.5 degrees centigrade. The animal was able to take this preparation without developing diarrhea. With this mixture the dog absorbed 83 per cent of the

TABLE II

*The Amount of Water in the Stools of a Dog Without a Stomach With and Without Tenth Normal Hydrochloric Acid in the Diet*

| Diet                            | No. I   |       | No. II  |       | No. III |      | No. IV  |       |
|---------------------------------|---------|-------|---------|-------|---------|------|---------|-------|
|                                 | Without | With  | Without | With  | Without | With | Without | With  |
| With or without acid            |         |       |         |       |         |      |         |       |
| No. of studies                  | 4       | 6     | 5       | 3     | 4       |      |         | 4     |
| Av. weight of moist stools      | 146.2   | 109.1 | 156.2   | 159.3 | 253.2   |      |         | 159.5 |
| Av. weight of dry stools        | 41.5    | 36.6  | 49.4    | 54.6  | 85.5    |      |         | 56.3  |
| Av. weight of water in stools   | 104.5   | 72.5  | 106.8   | 108.0 | 167.7   |      |         | 101.7 |
| Av. per cent of water in stools | 71.6    | 66.4  | 68.3    | 66.7  | 66.2    |      |         | 63.7  |

Diet No. I 350 grams meat, 100 grams of bread per day.  
 Diet No. II 350 grams meat, 100 grams bread, 50 grams lard.  
 Diet No. III 350 grams meat, 100 grams bread, 250 grams lard.  
 Diet No. IV 350 grams meat, 100 grams bread, 250 grams cream.

nitrogen and 89 per cent of the fat. (Metabolism determination 52).

Further studies of this kind should be made. The absorption of nitrogen was better than the average with both fresh pancreas and pancreatin and bile. The absorption of fat was lower with the pancreas and somewhat higher than the average with pancreatin and bile. But the index of absorption fluctuated so widely

TABLE III

*A Comparison of Motility, as Shown by Ingested Carmine, between 3 Normal Dogs and 2 Dogs without Stomachs on Different Diets*

| Dog            | Diet                            | Diet                                            | Diet                                             |
|----------------|---------------------------------|-------------------------------------------------|--------------------------------------------------|
|                | 350 gms. meat<br>160 gms. bread | 350 gms. meat<br>100 gms. bread<br>50 gms. lard | 350 gms. meat<br>100 gms. bread<br>50 gms. cream |
| Normal 1       | 48 hours                        | 48 hours                                        | 48 hours                                         |
| Normal 2       | 48 hours                        | 48 hours                                        | 96 hours                                         |
| Normal 3       | 18 hours                        | 48 hours                                        | 21 hours                                         |
| Pathological 4 | 24 hours                        | 24 hours                                        | 18 hours                                         |
| Pathological 5 | 36 hours                        | 24 hours                                        | 18 hours                                         |

in the pathological animals it is impossible to conclude much from single determinations of this kind.

Next, we fed the fat in the form of fatty acids and glycerine to determine whether the lack of absorption depends upon a failure to break down the neutral fat. Accordingly, Dog No. 5 was given a diet each day of 350 grams of meat, 100 grams of bread, 39 grams of fatty acids (obtained from lard) and 2.02 grams of glycerine per day. (See metabolism determination No. 55). The animal ate the diet well and from it absorbed 84 per cent of the nitrogen and 74 per cent of the fat. Therefore, absorption was no better when fatty acids were fed than when neutral fat was given.

*Motility* is another function of the intestinal tract that one would expect to be deranged by a gastrectomy; such proved to be the case. Powdered carmine (the substance chosen to delimit various stools) was recovered from the pathological animals in from 18 to 36 hours, in contrast to 21 to 96 hours from the normal dogs. (See Table 3). Carmine was obtained from the pathological dogs about two days sooner, on the average, than it was from the normal ones.

*Roentgenographic studies* threw more light on the nature of the increase in motility. (See Protocol). They revealed very definite dilatation, (later confirmed at autopsy), of most of the jejunum. This filled rapidly with the test meal, which the dog ate, in about 15-20 minutes. Hence, the upper intestine contained in a few minutes the same meal which left the stomach of the normal animals in from 4-5 hours. From 3½ to 4 hours the picture was not much different in the normal and abnormal animal. The barium had reached approximately the same distance in the small intestine. The only difference was that there appeared to be more barium in the intestines of Dog No. 5. The barium entered the cecum about the same time in both animals, namely, around 5 to 6 hours. However, it left the colon of the dog without a stomach more rapidly than it did that of the normal animal. One may say that, in the abnormal animal, food enters the intestine immediately. Once there, its passage through the small intestine is only slightly, if at all, accelerated. However, it leaves the colon more rapidly than normally. This rapid emptying of the colon could ac-

count for the fact that carmine came through more quickly in the dog without a stomach.

In order to determine the effect which the rapid passage of food into the jejunum might have on digestion, we tried feeding the dog small amounts at frequent intervals. By this means we could hope to distribute the food to the jejunum at about the same rate that the stomach normally does. Since the disturbance in digestion of the fat had been more marked than it had with the nitrogen, and since the stomach empties the fat more slowly than other food products, it seemed best to gauge the rate of feeding by the amount of fat in the diet. As a precedent for this, we had the work of Zawilski (21), who, in 1876, studied the absorption of fat by dogs. As he used animals of approximately the same size as ours (his weighed about 13 kg each), it was possible to determine from his figures that the stomach of an animal of this size discharged from 5 to 10 grams of fat per hour, and that the animal absorbed on the average about 6 to 7 grams an hour.

Therefore, at half hourly intervals we fed amounts of food which would introduce to the jejunum about 8 grams of fat per hour. Table 4 shows the result of feeding the diet slowly. Fractional feeding resulted in an absorption of fat varying from 92 to 98 per cent, with an average of 95 per cent.

The absorption of nitrogen was low, varying from 4 to 31 per cent with an average of 14. These very low figures were obtained on diets low in nitrogen and will be discussed more fully later on. But the table shows that absorption was better with slow feeding than when all the food was given at once.

## DISCUSSION

The results of this study are not easy to evaluate at first glance, and it is unfortunate that we were unable to repeat many of the studies. But several factors over which we had no control forced us to discontinue the work, before we had an opportunity to obtain conclusive answers on all the doubtful points. However, our study shows certain things.

Removal of the stomach can result in decreased digestion. The differences in the figures obtained on the normal and the pathological dogs are significant. The absorption of nitrogen by the normal animals was

TABLE IV

*A Comparison of the Absorption of Nitrogen and of Fat After Feeding Diets Slowly and Rapidly*

| Diet          | Method of Feeding | Per cent Nitrogen Absorbed | Per cent Fat Absorbed |
|---------------|-------------------|----------------------------|-----------------------|
| 75 gms. meat  | Fractions         | 7.0                        | 98                    |
| 50 gms. bread | Fractions         | 4.0                        | 94                    |
| 50 gms. lard  | Together          | Negative Balance           | 88                    |
| 175 gms. meat | Fractions         | 31                         | 92                    |
| 50 gms. bread | Together          | 15                         | 79                    |
| 50 gms. lard  | Together          |                            |                       |

less than 86 per cent in only one test, in which instance it reached a low point of 68 per cent. Since this was the only time that we obtained a figure on this dog different from the other normal animals, it seems justifiable to exclude it as being due to a technical error.

In contrast to these findings, the highest figure for the absorption of nitrogen on the pathological dogs

was 88 per cent. The animals without stomachs absorbed, on the average, 16 per cent less nitrogen than did the normals. The difference in the ability to handle fats was even more marked. The lowest absorption of fat by the *normal* animals was 87 per cent in contrast to the highest absorption by the *pathological*

TABLE V

*The Amount of Fat and Nitrogen Lost in the Stools Per Day in Relation to the Amount of Fat Fed Per Day*

| Fat in diet per day in grams | Grams of fat in stools per day |                  | Grams of N <sub>2</sub> in stools per day |                  |
|------------------------------|--------------------------------|------------------|-------------------------------------------|------------------|
|                              | Normal Dog                     | Pathological Dog | Normal Dog                                | Pathological Dog |
| 7.0                          | 0.52                           | 5.57             | 1.0                                       | 3.7              |
| 22.71                        | 0.63                           |                  | 0.52                                      |                  |
| 37.0                         |                                | 9.18             |                                           | 4.6              |
| 47                           |                                | 10.1             |                                           | 3.64             |
| 54                           | 0.37                           | 8.38             | 1.23                                      | 2.55             |
| 57                           | 0.91                           | 24.14            | 0.571                                     | 4.26             |
| 82                           | 1.00                           |                  | 0.85                                      |                  |
| 108                          | 0.62                           |                  | 0.93                                      |                  |
| 157                          | 2.31                           | 24.59            | 1.15                                      | 2.33             |
| 206                          | 0.61                           |                  | 0.63                                      |                  |
| 257                          | 3.49                           |                  | 0.84                                      |                  |

dogs of 86 per cent. The abnormal dogs absorbed on the average 38 per cent less fat. That there is a true disturbance in digestion is further supported by the fact that the dogs without stomachs had had no normal stools during the one to three years of observation.

A second important observation is that the absorption of food by the test animals varied over a greater range than it did in the normal. The figures show a variation for the normal animals of 12 per cent for both nitrogen and fat, as opposed to a variation for the pathological animals of 24 per cent for nitrogen and 69 per cent for fat. We may admit that some of this fluctuation may result from the occasional loss of fecal material. However, the difference between the pathological and control animals is sufficiently great as to be significant. Therefore, the failure of digestion would appear to depend upon something which fluctuates from time to time.

Moreover, the data show that this fluctuation is not the result *per se* of a variation in the amount of the foodstuffs which are exhibited. (See Table 5). Although the amount of fat in the stools of both the normal and the pathological animals increases with an increase of fat in the diet, this occurs with smaller amounts of fat in the case of the pathological animals. Table 6 clearly shows that the amount of fat in the diet does not influence the loss of nitrogen, as postulated by Burger and Konjetzny.

Now, if we turn to Chart 1, which enables us to visualize the results of the work more clearly, it is found that the assimilation of food was better after feeding certain "sham" digestive secretions.

Both the fat and nitrogen were absorbed slightly better when the animal was taking hydrochloric acid. In the one experiment in which fresh pancreas was given with the diet, there was a normal absorption of nitrogen, whereas the absorption of fat was markedly deficient. We have no explanation to offer for this apparent inconsistency. When pancreatin and dessicated bile were given together, the absorption of both fat and nitrogen definitely was higher. The fatty acids were absorbed to the same degree as was the neutral fat when hydrochloric acid was administered.

These results appear to conflict. The improvement in assimilation suggests that the failure of digestion may result from an inadequate supply of ferments. However, if this be true, one would expect the giving of pancreatic substance would improve the assimilation of fat as well as of nitrogen, and one might anticipate a better absorption of the fatty acids.

It is possible that some of the apparent inconsistencies are exaggerated by the amount of fluctuation which has been found to occur in the digestion of the dog without a stomach.

However, slow feeding gave a better assimilation of fat than did the administration of the sham digestive secretions and ferments, and, in fact, the absorption of fat was essentially normal. Since we introduced the fat to the intestines at approximately the same rate as it normally leaves the stomach (according to the figures of Zawilski), it becomes evident that the intestine must have supplied lipolytic ferments as fast as it is called upon to do under normal conditions.

Hence, it seems to be evident that, so far as the fat is concerned, the failure of digestion can be explained satisfactorily by the fact that, in the absence of the stomach, material enters too fast for the normal supply of lipolytic enzymes adequately to mix with the food. Also, we have shown that the upper part of the small intestine was dilated to a marked degree and therefore, it seems reasonable to suppose that this may be another reason for insufficient mixing of the food with the digestive secretions. In these conditions, the fat may be washed along without obtaining an adequate breakdown into its simplest components suitable for

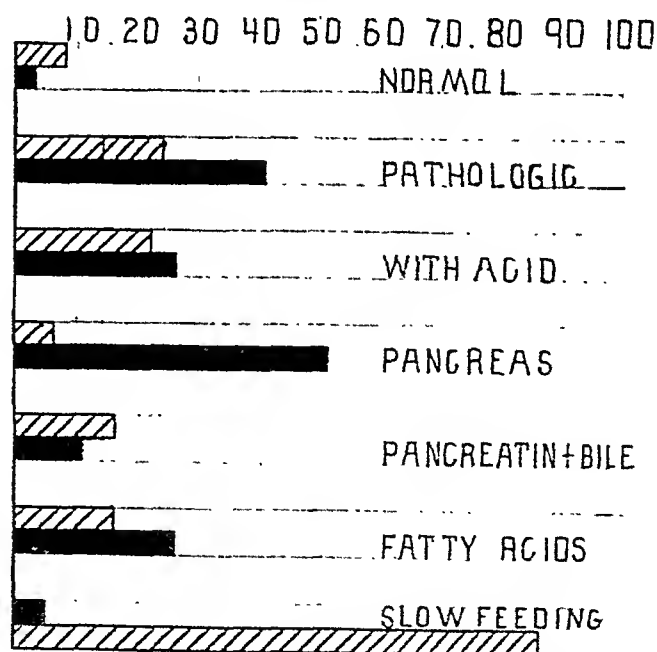


Chart 1. The amount of nitrogen and fat eliminated in the stools expressed in per cent of the quantity ingested. Solid black shows per cent of fat. Strip shows per cent of nitrogen.

absorption, when and if it comes into contact with the walls of the intestine.

It now becomes clear that the rate at which the animal ate the other diets will account for some of the hitherto unexplained discrepancies. He ate the mixtures of acid and pancreatin and bile (which had a

sour odor) more slowly than usual. This fact can explain why absorption was better when these substances were given, whereas, it would not be possible to explain the normal absorption of fat with slow feeding, if one assumed an inability to secrete a normal supply of lipolytic substances.

Chart 1 shows an apparent objection to these statements until the facts are understood. The absorption of nitrogen appears to be poorer with slow feeding than is usual. This depends upon two conditions, namely, the small amount of nitrogen in the diets used in the fractional feeding and the increased amount of nitrogen in the stools as a result of a chronic irritation.

As seen in Table 6 the intake of nitrogen was very small, it being per day, 3.62 grams in one diet and

TABLE VI

*The Amount of Fat and Nitrogen Lost in the Stools Per Day in Relation to Slow and Rapid Feeding*

| Nitrogen in diet per day in grams | Grams of fat in stools per day |               | Grams of nitrogen in stools per day |               |
|-----------------------------------|--------------------------------|---------------|-------------------------------------|---------------|
|                                   | Slow Feeding                   | Rapid Feeding | Slow Feeding                        | Rapid Feeding |
| 3.62                              | 2.09                           | 6.21          | 3.44                                | 4.42          |
| 6.36                              | 4.11                           | 11.89         | 2.28                                | 5.35          |
| Fat in diet per day in grams      |                                |               |                                     |               |
| 51                                | 2.09                           | 6.21          | 3.44                                | 4.42          |
| 53                                | 4.11                           | 11.89         | 2.28                                | 5.35          |

6.36 in the other. At the same time, the dog excreted a greater amount of nitrogen in his stool than normal because of chronic irritation resulting from a long continued indigestion. Hence, the fixed loss of nitrogen is higher than normal in the pathological dogs. Low values of nitrogen in the diet give an unduly low ratio to the nitrogen excreted in the stools. But Table 4 shows that slow feeding favorably influences the assimilation of nitrogen. The disturbed motility, therefore, interferes with the absorption of the nitrogen in the same way that it disturbs the absorption of fat.

The observations which we have made on these dogs serve to explain the variable reports in the literature concerning *digestion subsequent to gastrectomy*. Evidence for failure in digestion will depend upon the rate at which the food is eaten, the amount of dilatation which has developed in the intestine and the type of food that is eaten at the time of the study. The degree of dilatation is important, for the greater it is, the more food the patient can ingest before feeling filled. Hence, he will eat more food in a given time and may exceed the physiological rate at which the intestine can supply the required digestive secretions. Marked dilatation also may interfere with the mechanical treatment of the food, in respect to mixing and bringing it into contact with the walls of the intestine.

The more or less generally reported fact that the digestion of fat is interfered with to a greater extent than is the digestion of nitrogen is easy to understand, when one remembers that the stomach discharges fat more slowly than it does nitrogenous substances. This is evidence that the intestine is able to digest protein more rapidly than fat; if a mixture of food is allowed to enter the intestine too rapidly, the absorption of fat will suffer to a greater degree.

The relative proportion of nitrogen to fat in the diet also will influence the apparent efficacy of digestion of the two substances. If the intestine is overloaded by a mixture of food, in which one element largely outweighs the other, it is possible to have a situation in which one substance is supplied in excess of the intestine's ability to digest the product; whereas the amount of other substance may be within the physiological limits of digestion. Normally, the stomach regulates this condition by discharging the various food components at different speeds.

Finally, this study emphasizes the importance of the stomach as a distributor of the food to the intestine. As a result of the work of Cannon (22) and others, it has been known for a long time that different foodstuffs leave the stomach at different rates of speed. Yet clinicians have given less attention to this function than to that of secretion and digestion, in spite of the proof by Ogata and Schmidt and of Strassburger that gastric secretion and digestion are unimportant factors in the final utilization of food. Further study of the distribution of food by the stomach to the duodenum might be of distinct value.

### SUMMARY AND CONCLUSIONS

This paper reports a study of the digestion of two dogs upon which a total gastrectomy had been performed two years previous to the initiation of this investigation. The study shows an inability of these animals to utilize the nitrogen and the fat of the diet as effectively as did normal animals. The digestion of carbohydrates was not determined because the available methods of study were not satisfactory. Although fluctuations in the absorption of nitrogen and of fat occurred in both the normal and the pathological animals, the extent of this fluctuation was much greater in the pathological dogs. The maximum absorption of nitrogen and fat in the pathological animals never was more than the minimum absorption by the normal dogs. In general, the dogs without stomachs did not utilize the fat so well as they did the nitrogen.

It was found that, if the diet is fed slowly so that the fat enters the duodenum at the approximate rate at which it leaves the normal stomach, the absorption of fat is normal. Also this slow feeding results in better absorption of nitrogen than when the diet is eaten rapidly. This would appear to show that the intestines are capable of utilizing fat as effectively and rapidly as they are called upon to do under normal conditions. It is suggested that the slight improvement in digestion which follows the administration of hydrochloric acid and of digestive enzymes results from a slower rate of food ingestion. It is further suggested that the amount of intestinal dilatation which occurs following removal of the stomach, determines the efficiency of digestion by influencing the rate at which a patient can eat. The study emphasizes the importance of the stomach as a regulator of the rate at which the different foodstuffs reach the intestine.

### REFERENCES

1. Gabrila, J., and Danicico, J.: Digestion of Fats and Proteins Following Resection of Stomach. *Arch. des Mal. de L'App. Digest.* 19:587, May, 1929.
2. Czerny, V., and Kaiser: Beiträge z. operativen Chirurgie. Stuttgart, 141, 1878.
3. Carvallo, J., and Pachon, V.: Studies on the Digestion of a Dog Without a Stomach. *Arch. de physiol. norm. et path.* 6:106-112, 1894.

4. Connor, P. S.: Society Proceedings, Cincinnati, Academy of Medicine—in the *Medical News*, 45:578, Nov. 22, 1884.
5. Schlatter, C.: A Unique Case of Complete Removal of the Stomach; Successful Oesophago-enterostomy; recovery. *Med. Rec.*, N. Y., 16:273-275, 1897.
6. Stahnke, E. N.: Concerning Total Removal of the Stomach. *Zentralbl. f. Chir.*, 60:865-870, April 15, 1933.
7. Ducuing, J., Soula C., and Fränkel, B.: Total Gastrectomy in Man. *J. de Chir.*, 44:175-210, Aug., 1934.
8. Hofmann, A.: Studies on Nitrogen Metabolism Following Complete Removal of the Stomach. *Munch. Med. Wchnschr.*, 45:560, May 3, 1898.
9. Heilmann, P.: Metabolism After Resection of Stomach. *Munch. Med. Wchnschr.*, 72:178-182, Jan. 30, 1925.
10. Troell, A., Losell, S., and Karlmark, E.: A Case of Total Gastrectomy for Cancer. *Mitt. a. d. Gvcrzgeb. d. Med. u. Chir.*, 40:542-549, 1927.
11. Solowiew, L.: Nitrogen Metabolism in Man Following Complete Resection of the Stomach. *Biochem. Zeitschr.*, 199:121, 1928.
12. Shima, K.: Studies on General Metabolism Following Total Extirpation of Stomach and Following Extensive Resection of Intestine. *Beitrag. zur Klin. Chir.*, Berlin, 153:275, Aug. 22, 1931.
13. Bürger, M., Konjetzny, G. E.: Concerning the Utilization of Food After Total Extirpation of the Stomach. *Zentralbl. fur Chir.*, 19:1154, 1929.
14. Von Haberer, H.: Results of Extensive Resection and Total Extirpation of Stomach. *Deutsch. Med. Wchnschr.*, 56:562, April 4, 1930.
15. Drevermann, P.: A Contribution on the Subject of Total Resection of the Stomach. *Deutsch. Zeitschr. f. Chir.*, Vol. 154: 144-168, 1920.
16. Schwartz, E.: Total Extirpation of Stomach. *Zentralbl. f. Chir.*, 53:578-584, 1926.
17. McCrudden, F. M.: A New Technique in Metabolism Experiments. *Journ. of Med. Research*, 9:135, 1903.
18. Folin, O., and Wentworth, A. H.: A New Method for the Determination of Fat in Feces. *Journ. Biol. Chem.*, 7:421, 1910.
19. Ogata, M.: Concerning the Digestion After Elimination of the Stomach. *Archiv. f. Physiol.*, Leipzig, 1:89-116, 1883.
20. Schmidt, A., and Strassburger, J.: The Feces of Man Under Normal and Pathological Conditions. A. Hirschwald, Berlin, 1905.
21. Zawilski: The Amount and Duration of the Chyle Passing Through the Thoracic Duct After the Ingestion of Fat. *Arbeiten A. D. Physiol.*, Anstalt, 149, 1876.
22. Cannon, W. B.: The Passage of Different Food Stuffs From the Stomach and Through the Small Intestine. *Am. Jour. Physiol.*, 12:387-418, 1906.

#### DISCUSSION:

FRANKLIN W. WHITE (Boston): This paper is well planned and carefully worked out, and ought to clarify our ideas of what happens to the functions of the digestive tract after a total gastrectomy. The paper is doubly welcome, since most recent studies after gastrectomy have been of the blood, not of the digestion.

I wish to make a mild objection to the method of measuring the absorption of food. There may be a source of error in weighing the food and in analyzing the stool for nitrogen and fat, and calling the difference the amount absorbed: *First*, the gastrointestinal tract is a secreting as well as an absorbing organ; that is, some nitrogen is added in addition to that given in the food; *Second*, the food nitrogen may be reduced in the stool not because it is absorbed, but because it is destroyed by enzymes or bacteria. In spite of these objections it is probably the best method we have at present.

We get a sidelight on this question of digestion by the study of other cases where there is lack of gastric secretion or changes in emptying time of the stomach. Take the first group of achylia or pernicious anemia. Here there is no HCl in the stomach, and the emptying time is more or less normal. Our stool studies with the Schmidt-Strassburger test diet and rough quantitative methods have shown that the proteid digestion is complete, and the nitrogen output in the stools is normal, and the patient's nutrition is good as a rule, even when under observation for six or seven years or more. On the other hand, if a motor change occurs, such as diarrhea, there at once appears a large nitrogen loss in the stool.

In subtotal gastrectomy for gastric ulcer or cancer we have both lack of HCl in the stomach and some motor changes. The X-ray shows a funnel-shaped stomach with no peristalsis, and *rugae* coarser than normal in the stomach and duodenum. At first the stomach empties rather rapidly in twenty to sixty minutes, depending on the kind of operation. Later it tends to empty periodically in one to one and one-half hours. The upper jejunum is dilated to two or three times normal size, and there is

small intestine hurry, so that the meal reaches the lower ileum in one-half to two hours. At first all these patients take small frequent feedings. Later most cases gradually take ordinary feedings. The stools are approximately normal unless there is diarrhea, which causes at once increased loss of nitrogen and fat. In the third group of total gastrectomy I have seen only two patients, both cancer, sick and anemic, and rather short-lived, and it is impossible to say that any changes observed were due to the gastrectomy alone.

All this data bears out Dr. Emery's idea that the cause of faulty digestion after gastrectomy is not lack of secretion and proteid digestion, but is largely due to changes in motor function, such as the rapid emptying of the stomach and the dilation and hurry in the upper small intestine, and secondarily to changes in absorption.

I agree with Dr. Emery's explanation that the variable data of other authors on digestion after total gastrectomy may be largely due to such variable factors as ordinary feeding in one case and small, frequent feeding in another: the degree of accommodation changes in the bowel, whether early or late, such as dilatation and increased motility; perhaps also to a third factor which Dr. Emery did not mention—the degree of the anemia. I am not speaking of pernicious anemia, but the hypochromic, microcytic type. The anemic group after gastrectomy is largely a group of surgical failures with pain, gas, vomiting, diarrhea, etc., which often lead to deficient diets.

Finally, it is evident that the stomach is not indispensable as a reservoir or a ferment-producer, and that the necessity for HCl to stimulate intestinal secretion has been greatly exaggerated. Dr. Emery is to be congratulated on an excellent and useful piece of work.

DR. LEON BLOCH (Chicago): Dr. Emery's report of an excellent piece of work coincides fairly well with the clinical phenomena in the wake of subtotal resection of the stomach for peptic ulcer. Especially interesting is that phase of the work dealing with the reduction in digestion of fats. This undoubtedly contributes to the failure of some patients to gain weight, post-operatively, and may, as has been stated, occur both after resection and gastroenterostomy.

While this discussion should be limited primarily to experimental work, I have had no such experience and will therefore refer to clinico-physiologic data which bear out the findings of the essayist. The symptoms which manifest themselves after resection are mainly of a three-fold character, the results of jejunal overdistention, too rapid propulsion of the intestinal contents and occasionally a sort of indigestion ascribable to lack of hydrochloric acid.

Normally the jejunum receives its contents in small quantities from the duodenum. After resection, large quantities of poorly comminuted food enter the jejunum in a short time and over distend it. The subjective symptoms which result from the ensuing irritation of the intestinal sympathetic nerves are fulness, faintness and perspiration coming on a short time after eating; such may recur over a period of months, eventually to disappear, or, in a few instances, recur for a year or more, especially in cases of resection of a high lying gastric ulcer on the lesser curvature.

Diarrhea is a frequent symptom after resection and may be accompanied by cramps, particularly so, if a high residue diet is partaken of too early. Dr. Emery has called attention to shortening of the time of the intestinal passage of food as one of the causes of faulty digestion. This is of particular interest because two of the points mentioned by the essayist are encountered clinically. One is that experience has shown that frequent feedings of small amounts of comminuted low residue food decrease peristaltic activity. This therapeutic measure is not unknown and has resulted in considerable improvement in the nutrition of the patient.



The second point is the last one in my discussion and refers to symptoms which for some reason or other are relieved by the administration of hydrochloric acid. It is a peculiar thing that the lowered or apparently absent acidity, which is one of the *desiderata* of resection should lead to symptoms of indigestion after the operation and which in some patients are relieved by hydrochloric acid. Dr. Emery has noted an increase in the absorption of the diet after the administration of hydrochloric acid and thereby confirmed clinical experience. It may be given after meals, before meals, or both. Not only is there relief of the distress but also there is an increase in weight as a result of the improved digestion.

DR. EDWARD S. EMERY, Jr. (closing the discussion): I should like to apologize for having presented

this work in a way that might appear as though it was not finished, and it really wasn't—in, that further work should have been done on the absorption of nitrogen, but, unfortunately, the laboratory was about to undergo repairs by carpenters and plumbers, and I had to stop before I could finish to my satisfaction the study of the nitrogen factor.

What Dr. Bloch says about hydrochloric acid is interesting in that von Haberer and one other European have reported definite diarrhea following total gastrectomy, which was controlled by the administration of hydrochloric acid. I do not know just why that should be so. I should like to know.

I wish to thank Dr. White and Dr. Bloch for discussing this paper.

## Experimental Studies in Gastric Physiology in Man: the Mechanism of Gastric Evacuation After Partial Gastrectomy as Demonstrated Roentgenologically\*

By

HARRY SHAY, M.D.

and

J. GERSHON-COHEN, M.D., MSe. (Med.)

PHILADELPHIA, PENNSYLVANIA

LITTLE over a half century has elapsed since Billroth (1) performed the first successful resection of the pylorus in man. Since then, many contributions concerned with the resulting altered gastric physiology have been made. Most investigators, however, have been occupied rather with the changes in gastric chemistry than with the altered motor function which has been considered, clinically, the result of another "dumping operation." We have been unable to find any studies in man which show whether or not any real alteration in the mechanism of gastric evacuation occurs after partial resection. Our data demonstrate that if the resected stomach be properly classified with regard to its gastric secretory change and compared with an intact stomach of corresponding secretory response, the alteration in the behavior of the gastric-emptying mechanism will be only quantitative. Our comments refer only to the Billroth I and Polya types of resection. The Billroth II type will be considered in our studies of the gastroenterostomized stomach, since this resection presents essentially the problem of a gastroenterostomy with the pyloric end of the stomach occluded.

### EXPERIMENTAL METHOD

This report is based on sixty-seven serial X-ray examinations performed on six cases of partial gastrectomy. The method of investigation was identical with that recorded for our previous studies (2). The patients studied had had partial gastric resections at periods varying from one-and-one-half to six years

previously and who, at the time of the investigation, after a complete diagnostic survey, appeared to be in good health. All patients exhibited a complete anacidity by fractional gastric analysis following the usual Ewald meal.

Intubations, both gastric and jejunal, were repeated to eliminate any psychic disturbance. Standard conditions for the studies were maintained. The evening was selected for the examinations because of its convenience. The patient was permitted to eat his usual luncheon at noon, but at 3 p. m., three slices of dry toast and a cup of tea without cream were taken. Nothing was taken thereafter until 8 p. m., when the studies were begun.

The X-ray test-meal consisted of 250 c.c. of tap water at 38° C. containing two ounces of barium sulphate. All test substances in this group of experiments were added to the water-and-barium meal, the total volume remaining constant. Gastric emptying-time, for each subject under the standard conditions, was determined with the water-and-barium meal. This was checked by a second study and rechecked at the completion of all the tests.

The emptying-time for the water-and-barium meal having been established, new studies were made in which various test substances were introduced: hydrochloric acid (0.09 to 0.49%), sodium bicarbonate (1% and 5%), glucose (5% to 40%), normal saline, 5% sodium chloride, varying amounts of olive oil, and meals of milk and of cream. The effects on gastric motor function were studied serially by fluoroscopic and roentgenographic examinations. Observations and records were made during the first five minutes after ingestion of the meal and at fifteen minute intervals until gastric emptying of the water-and-barium meal had occurred. With the other test substances, studies of the residues were continued up to the

\*Read at the 38th Annual Session of the American Gastro-Enterological Association, Atlantic City, N. J., June 10-11, 1935.  
Approved by the Publications' Committee of the Association.



emptying-time noted for the water-and-barium meal alone.

The group was then studied for the effects of the same agents upon the gastric-emptying of the standard water-and-barium meal when they were applied directly to the intestinal mucosa. The intestine was first intubated with a Rehfuß tube. The test agent was then slowly instilled into the intestines while the water-and-barium meal was taken. The intestinal instillation was regulated with a Murphy bulb. Before applying the various agents, however, gastric evacuation was determined after intestinal intubation alone, in order to note any mechanical effect of the tube. As recorded for intact gastro-duodenal segments, no change in gastric evacuation resulted from the mere presence of the tip of the tube in the jejunum and of the tube through the stoma. Serial roentgenographic data were recorded as before.

### EFFECTS OF ACIDS AND ALKALIES

A recent publication (2) reported data that show the effects of acids and alkalies on gastric-emptying in apparently normal individuals with the gastro-intestinal tract intact. Those agents were of concentrations similar to the ones used in the present experiments. Their effects were studied after ingestion by mouth and after direct instillation into the duodenum. From these studies, it was concluded that with an intact gastro-intestinal tract the pylorus is the local mechanism which determines gastric evacuation; that the local stimuli activating this mechanism arise from the intestinal mucosa and that the gastric hydrochloric acid is the normal intrinsic agent which, upon its arrival into the duodenum, acts as the mucosal stimulant.

It must be remembered that this summarized report was concerned with the *intact* gastro-intestinal tract; that it considered only the local mechanism involved, and did not mean to imply that gastric-emptying could not be modified by stimuli from remote areas, as, for example, inflammatory disease of the ileo-cecal region, pelvis, etc., or by some psychic factor. Further, it stressed the fact that gastric hydrochloric acid is not the sole agent that can stimulate the intestinal mucosa but that ingested foods through their physical or chemical properties are usually efficacious stimulants. Of especial interest from this standpoint is the recent contribution of Johnston and Ravdin (3). These investigators, from studies of the effects of various concentrations of glucose on gastric-emptying in the dog, found that when hypertonic solutions of glucose were placed in the stomach, gastric-emptying was delayed. Although the concentration of glucose in the stomach in many instances remained high, that in the jejunum and ileum was always at or below isotonicity. They believe that the small amounts of hypertonic glucose which pass into the duodenum offer the stimulus to pyloric activity and gastric retention. Thus, Johnston and Ravdin, by an entirely different experimental approach, reach a conclusion similar to that deduced from our roentgen studies in man. This explains probably why patients with achlorhydria may so frequently escape symptoms suggesting any marked disturbance of gastro-intestinal motility.

The importance of considering the acid secretory response of the individual under investigation, especially in studies with acids and alkalies also has been pointed out (2). It would be impossible to interpret the results obtained were this response unknown.

All the patients who had had a partial gastric resection showed a complete anacidity in response to the Ewald and to the water-and-barium meals. The motor phenomena observed in these subjects after the various stimuli ingested or applied directly to the jejunal mucosa, were identical with those obtained in the intact achlorhydric stomach, except quantitatively.

The gastric-emptying of the standard water-and-barium meal in our normal group was more rapid in the achlorhydrics than in those who had normal or hyper-acidity. This is, of course, the usual observation in uncomplicated cases of anacidity. The anacid, resected group emptied the same meal even more rapidly than did the intact achlorhydric stomach. Thus, the group of achlorhydrics with stomachs intact emptied the standard water-and-barium meal in periods ranging from fifteen minutes to one-and-one-half hours, but in the resected group, the gastric-emptying time for a similar meal in no case exceeded thirty minutes.

A similar relationship was found when the test substances caused delay in gastric evacuation. Less delay was observed in the resected achlorhydric stomach when the test substance either was ingested or applied directly to the intestinal mucosa. These observations confirm, in the human subject, what McCann (4) clearly demonstrated in the dog. He found that the stomach from which the sphincter had been removed was able to retain the test meal successfully. However, there were smaller quantities of material retained in similar time periods, thus indicating that the efficiency of the mechanism for the proper retention of the meal had been impaired. The results of the studies of Thompson (7) also are very significant at this point. He found, in dogs, after graduated multiple resection of the stomach with a Polya gastro-jejunosomy, that the acid values of the gastric contents, subsequent to the ingestion of his standard test meal, varied indirectly with the amount of the pylorus removed. Free hydrochloric acid failed to appear only after removal of the entire pyloric antrum of the stomach. In the roentgenologic observations on the emptying rate of the stomach following these operations the rate was found to be more rapid than pre-operatively, regardless of the grade of resection. Absence of the pyloric sphincter, therefore, rather than the increase in diameter of the pyloric outlet, would seem to be responsible for the result observed.

The fact that a stomach, after a resection of the distal end, is capable of retaining its contents in a manner resembling that of the intact stomach, seems to indicate that the pylorus is not the sole mechanism which regulates gastric evacuation. Yet such evidence does not necessarily deny to the pylorus a determining rôle in gastric evacuation in the intact stomach. It may well be that the other gastric muscle-fibers in the distal end of the resected stomach attempt to compensate for the loss of the pylorus. Such a view is supported by the facts that a resected stomach is less efficient in retaining its contents than is an intact stomach, and that the antrum, pylorus and duodenal "cap" behave, from a motor standpoint, as a physiologic unit. The latter has been indicated in the work of Cole (6), Wheelon and Thomas (5), as well as in the experimental studies of McCann (4), Thompson (7), ourselves (2) and others. For example, we found that, in the intact stomach, adequate stimuli applied to the intestinal mucosa always produced pyloric

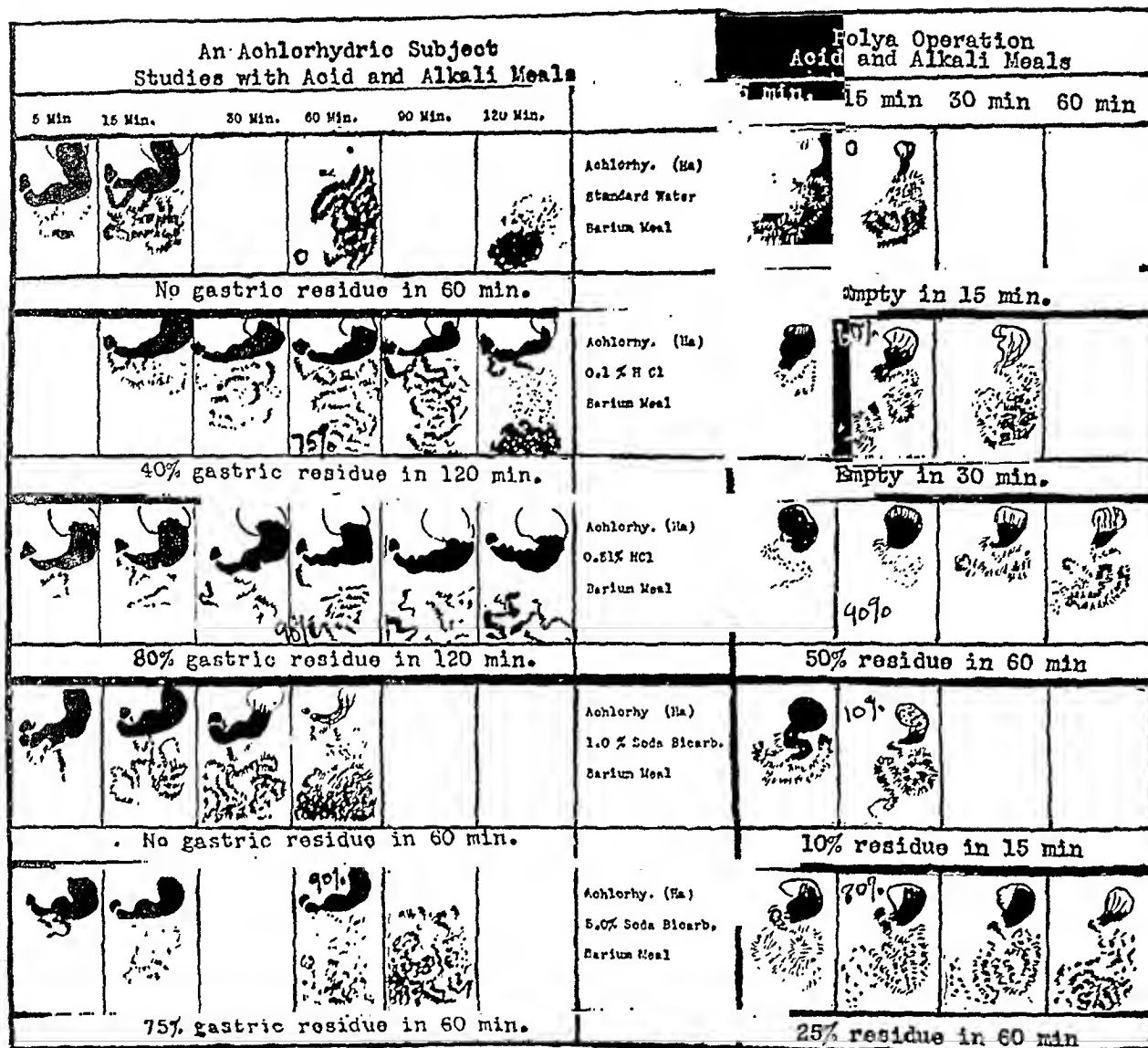


Fig. 1

closure, but antral spasm only when the stimulus was intense. We are disposed to believe from these facts that the remaining fibers act as a substitution mechanism to retain the gastric contents after pyloric resection. Too, they explain both the lesser efficiency of the mechanism and our observation that a stronger stimulus must be applied to the intestinal mucosa after pyloric resection to produce a retention of the gastric contents similar to that obtained in the intact stomach. The latter was especially apparent with the milder types of stimulant which produced relatively slight changes in gastric motility. With very strong stimulants, this difference was much less obvious or was lost entirely because they apparently (the stimulants) could call forth a maximum reaction in the mechanism of both the intact and the resected stomachs. Such reactions frequently were observed when 0.5% hydrochloric acid was applied directly to the intestinal mucosa.

Another question which must be kept in mind in this connection is whether the same stimulus, applied

to different portions of the intestinal mucosa, will equally activate the intestino-pyloric mechanism. Marbaix (8), in 1898, starting with the supposition that the intestine influences the action of the pylorus, attempted to determine the extent of intestinal mucosa from which this influence could be elicited. In his studies on dogs, Marbaix made one intestinal fistula at 10 to 15 cms. distant from the pylorus and others at varying points distal to the first along the course of the small intestine. He obtained clear evidence of the intestinal influence on the action of the pylorus when the mucosa of the upper half of the small intestine is stimulated. It may be, therefore, that the lower in the intestines the mucosa is stimulated, the stronger the stimulants necessary to produce similar gastric effects. In the resected stomach, not only has the pylorus been removed, but the segments of intestine which receive the gastric content are much lower than when the stomach is intact. In our studies on the normal intestinal tract by intubation with long tubes, we found that the delay of gastric evacuation varied

inversely to the distance from the pylorus at which the stimulant was applied.

### THE EMPTYING OF FATS AND HYPERTONIC SOLUTIONS

The observation that fat in the upper digestive tract decreases gastric motor activity was made by Ewald and Boas (9) in 1886. This has since been repeatedly confirmed. In 1901, Lintvarev (10), working in Pavlov's laboratory, published very interesting data of the effect of fats on gastric evacuation. Experimenting on dogs, who had both stomach and duodenal fistulae, and using olive oil, cod liver oil, butter, egg yolk, and cream, he found, in 150 experiments, that the pylorus closed as soon as oil passed into the duodenum. He concluded that fats introduced into the duodenum reflexly close the pylorus and do not permit any liquid to pass from the stomach for a considerable time. Recently, from roentgen studies on human subjects, we (11) came to the same conclusions, except as modified by the recent evidence that a humoral as well as a nervous reflex factor may activate the mechanism. Of particular interest here are the contributions of Quigley, Zettleman and Ivy (12); of Quigley and Phelps (13); of Ivy and Farrell (14); of Kosaka and Lim (15). The rapidity with which pyloric closure, the cessation of gastric evacuation and diminution and disappearance of gastric peristalsis, and often, antral spasm, follow the duodenal instillation of fats or any other equally active stimulant, forces one to suppose a nervous reflex mechanism. Yet the investigations of Quigley, Zettleman, and Ivy (12) clearly show that the nervous mechanism can not be the only one involved. These investigators, working with dogs and with entire stomach pouch preparations after complete denervation, found that total gastric inhibition followed the duodenal introduction of fatty substances. It is especially interesting to observe that the various fatty substances (12) and carbohydrates (13) were without effect upon gastric motility when applied to the gastric mucosa alone.

More recently, Quigley and Phelps (13), using auto-transplanted denervated pouches, were able to demonstrate similar phenomena following the arrival of carbohydrates in the upper intestines. In 1905, Carnot and Chassevant (17) (18), studying the effect of saline and glucose solutions on gastric-emptying in dogs with duodenal fistulae, came to very definite conclusions regarding the rôle of the osmotic pressure of solutions upon gastric evacuation. Isotonic solutions, they found, produced a series of pyloric openings which permitted the solutions to course very rapidly by successive jets from the stomach into the intestines without undergoing great modification. If, however, the solutions were appreciably far from isotonicity, the contact of the first portion of the liquid with the duodenum provoked reflex closure of the pylorus; this did not reopen until proper dilution of this portion had taken place. Carnot and Chassevant speak of this phenomenon as the "reflex delta-regulator" of the pylorus. Recently, Ravdin, Johnston, and Morrison (19), studying the concentrations of glucose in the stomach and intestines of the normal dog after intra-gastric administration, found that the introduction of hypertonic solutions was followed by an increase of volume and a decrease of concentration in the stomach, while the concentration of glucose in the intestines was approximately isotonic or lower at all times, re-

gardless of the concentration in the stomach. Later, Johnston and Ravdin (3), on the basis of these findings, suggested that the hypertonic solutions of glucose left the stomach slowly enough to permit their change to those fluid concentrations which would be acceptable to the intestines. This "control" was due to the reaction of the pylorus to stimuli from the duodenum caused by the small amounts of hypertonic glucose solution reaching it.

We have reported, for man, that the stimulation of the duodenal and upper intestinal mucosae by hypertonic and hypotonic solutions of electrolytes and non-electrolytes can produce pyloric closure, cessation of gastric peristalsis and evacuation (2). Although Quigley and Phelps (13) obtained gastric inhibition with approximately isotonic solutions of dextrose, it is worth noting that their results were "more striking, more conclusive and more constant when solutions of higher concentration (20% to 50%) were used." By our method of investigation we were unable to demonstrate any motor changes from the use of isotonic solutions. Quigley and Hallaran (16) also failed to cause any gastric motor depression with isotonic sodium chloride solutions.

In our studies, we found that the resected stomach responded to fats and to solutions of different osmotic pressures in a manner entirely comparable with the behavior of the intact stomach, but that these agents did not delay gastric-emptying to the same degree in a resected stomach as they did in the intact stomach.

### SUMMARY

Partial gastric resection apparently causes no basic changes in gastric evacuation. If the altered gastric chemistry which results from the resection is taken into consideration, then gastric evacuation is modified in the same way by the same agents that modify gastric-emptying of the intact stomach to a similar chemical response, except, of course, for quantitative differences. These differences appear to be due to the loss of the pyloric sphincter. The remaining gastric muscle-fibers appear to offer a substitution mechanism, but are not so efficient as was the pylorus. The response is similar to that of the intact stomach whether the test substances are ingested or are applied directly to the intestinal mucosa. The evidence also indicates that, even in a partially resected stomach, the mechanism of gastric evacuation is controlled from the intestinal side.

Since the stomach in this group was cut away from the duodenum, the intestinal effect upon gastric emptying cannot be dependent upon a reflex through the enteric plexuses. It does not however, rule out a long autonomic reflex. The data also indicate that resection of the stomach is in no real sense a "dumping operation" and that the roentgenologist in comparing gastric emptying times must take into consideration the nature of the meal used for the study.

### REFERENCES

1. Billroth, T.: In a Letter to the Editor. *Wien. Med. Wchnschr.*, 31, 162, 1881.
2. Shay, H., and Gershon-Cohen, J.: Experimental Studies in Gastric Physiology in Man. II. A Study of Pyloric Control. The Roles of Acid and Alkali. *S. G. O.*, 58, 935, (June) 1934.
3. Johnston, C. G., and Ravdin, I. S.: The Effect of Varying Concentrations of Glucose on the Emptying Time of the Stomach, both Normal and after Various Gastric Operations. *Ann. Surg.*, 101, 500, (Jan.) 1935.
4. McCann, J. C.: Studies on the Emptying of the Stomach. *Amer. J. Physiol.*, 89, 497, 1929.
5. Wheelon, H., and Thomns, J. E.: Observations on the Motility of the Duodenum and the Relation of the Duodenal Activity to that of the Pars Pylorica. *Amer. J. Physiol.*, 59, 72, 1922.

6. Cole, L. G.: Motor Phenomenon of the Stomach, Pylorus, and Cap Observed Roentgenographically. *Amer. J. Physiol.*, 42, 618, 1917.
7. Thompson, H. L.: Resection of the Pylorus. Its Effect on the Secretary and Motor Functions of the Stomach. Thesis Mayo Foundation, 1930.
8. Marbnix, O.: Le Passage Pylorique. *Cellule* 15, 249, 1898.
9. Ewald, C. A., and Boas, J.: Beiträge zur Physiologie und Pathologie der Verdauung. *Arch. Path. u. Anat.*, 104, 271, 1886.
10. Lintvarev, S. I.: The Role of Fats in the Passage of the Stomach Contents into the Intestine. Diss. Imperial Academy, St. Petersburg, 1901, No. 8 (In Russian).
11. Gershon-Cohen, J., and Shay, H.: Experimental Studies in Gastric Physiology in Man. III. A Study of Pyloric Control: The Role of Milk and Cream in Normal Subjects and in Those with Quiescent Duodenal Ulcer. In press.
12. Quigley, J. P., Zettleman, H. J., and Ivy, A. C.: Analysis of the Factors Involved in Gastric Motor Inhibition by Fats. *Amer. J. Physiol.*, 108, 643, (June) 1934.
13. Quigley, J. P., and Phelps, K. R.: The Mechanism of Gastric Motor Inhibition from Ingested Carbohydrates. *Amer. J. Physiol.*, 109, 133, (July) 1934.
14. Ivy, A. C., and Farrell, J. I.: Contributions to Physiology of Gastric Secretion. *Amer. J. Physiol.*, 74, 639, 1925.
15. Kosaka, T., and Lim, R. K. S.: On the Mechanism of the Inhibition of Gastric Motility by Fat. An Inhibitory Agent from the Intestinal Mucosa. *Chines. J. Physiol.*, 7, 5, 1933.
16. Quigley, J. P., and Hallaran, W. R.: The Independence of Spontaneous Gastro-Intestinal Motility and Blood-Sugar Levels. *Amer. J. Physiol.*, 100, 102, 1932.
17. Carnot, P. et Chassevant, A.: Modifications Subies, dans l'Estomac et le Duodenum, par les Solutions Salines, Suivant leur Concentration Moléculaire. Le Reflexe delta Régulateur du Sphincter Pylorique. *Comp. Rend. de la Soc. de Biol.*, 58, 173, 1905.
18. Carnot, P. et Chassevant, A.: Sur le Passage Pylorique des Solutions de Glucose. *Comp. Rend. de la Soc. de Biol.*, 58, 1969, 1905.
19. Ravdin, I. S., Johnston, C. G., and Morrison, P. J.: Comparison of Concentration of Glucose in the Stomach and Intestine After Intragastric Administration. *Proc. Soc. Exp. Biol. and Med.*, 30, 955, 1933.

### DISCUSSION:

DR. M. J. WILSON (Toronto, Ont.): This paper is of great interest to me because the Authors have adopted a method which I abandoned some years ago. In my experiments on normal subjects the presence of the tube in the duodenum hastened gastric evacuation.

It is of interest to compare this communication with the Authors' previous paper on the normal stomach. In both cases strong acid in the duodenum delayed gastric emptying to a marked degree. This is in accord with many experiments on dogs.

The Authors do not state how extensive the resections were in their subjects. This is a point of considerable importance, because after extensive gastric resection there is usually very little peristalsis observable. Dr. Singleton has recently examined four duodenal ulcer patients who had had Billroth I operations, in each case with less than an inch of stomach removed. Thus the operations could be termed pylorotomies. Under the fluoroscope, gastric peristalsis was just as marked as before operation, and the stomach appeared to empty in exactly the same way as previously, and at the same rate. In two of the cases it was almost impossible to tell by fluoroscopic examination that any operation had been performed. Thus the removal of the pyloric sphincter had very little effect on the progress of the meal.

The Authors infer that, in the normal stomach, it is contraction of the sphincter which delays gastric emptying. I cannot agree with this. Thomas, Crider and Mogan made a very significant observation when they stated that irritation of the duodenum apparently delayed gastric evacuation not by contracting the pyloric sphincter but by decreasing gastric peristalsis. In my opinion the best of the available evidence tends to confirm this view.

I should like to ask the Authors if they made any observations on gastric peristalsis in these cases.

DR. JOHN P. QUIGLEY (Cleveland, O.): Consideration of the physiology of gastric evacuation emphasizes the existence of a mechanism well calculated to insure slow emptying of the stomach and prevent overloading of the intestine, especially with unsuitable material. The factor of safety is pronounced. Primarily, gastric emptying depends: first on a pressure within the stomach greater than is the intraduodenal pressure, produced essentially by gastric motor activity; second, on the "stop-

cock action" of the pyloric sphincter. Each of these mechanisms is controlled from the proximal intestine by reflexes and probably also by humoral factors, *c.g.*, by "enterogastrone."

Other factors modify gastric evacuation, usually to a minor extent and need not be emphasized in the present discussion.

The observations of Drs. Shay and Gershon-Cohen on gastric evacuation following pyloric resection are quite in accord with the above analysis. They have demonstrated that when the pyloric sphincter is removed, suitable substances in the intestine may still retard gastric evacuation.

The studies of Quigley, Zettleman and Ivy, and of Quigley and Phelps are pertinent to this subject. They observed motor inhibition of the pyloric-obstructed stomach when fats or sugars were introduced into the jejunum. Since this phenomenon could also be demonstrated following denervation of this stomach preparation, the humoral mechanism must be involved.

Applying these results to the investigation of Drs. Shay and Gershon-Cohen it appears evident: (1) that a humoral mechanism is involved in the retarded emptying of the pylorotomized stomach, (2) it operates by depressing gastric motility, (3) this inhibition is initiated by the presence of suitable substances in the upper intestine, and (4) hydrochloric acid is not essential for the initiation of this mechanism.

DR. HARRY SHAY (closing the discussion): Dr. Wilson, we have in the course of our gastric motor studies in the past five years utilized some fifty or sixty patients. In all cases have we studied the effect produced by the tube alone. In neither the intact gastro-duodenal segment with the tube through the pylorus, or in the resected stomach with the intestine intubated by way of the stoma, have we noted any material change in the gastric emptying time of the standard water and barium when compared with the results obtained in the absence of the tube.

(Slide): (See Fig. 1). These are representative pen and ink drawings made from the X-ray photographs and illustrate the effects of the various meals then ingested. The group on the left shows the results obtained in an achlorhydric subject with an intact gastro-intestinal tract. The right group picture similar studies in a case after partial gastrectomy. The upper line of drawings represents the results obtained in each with the standard water and barium meal. We note, for example, that the emptying time in this instance was sixty minutes for the intact tract. The same individual after the ingestion of a 0.1% hydrochloric acid solution showed a gastric residue of 40% at the end of two hours. This is of interest since a 0.1% hydrochloric acid solution certainly is physiological for the upper duodenum.

In the second row, we find the results obtained in the same patient following a meal of 0.51% hydrochloric acid. We see a much greater residue at twice the normal emptying time. The 1% sodium bicarbonate (essentially an isotonic solution) produces no effect in the achlorhydric. This meal in the individual with normal or hyperacid response, shortened the gastric emptying time as compared with that obtained with the standard water and barium meal. You will note, however, that the 5% sodium bicarbonate meal (a hypertonic solution) caused a 75% gastric residue at sixty minutes at which time the standard water barium and 1% bicarbonate meals had been emptied.

On the right we note that in this resected stomach the 0.1% hydrochloric acid doubled the emptying time of the standard water and barium meal while the 0.5% meal more than quadrupled the same period. The isotonic bicarbonate again caused no material change, while the hypertonic (5%) bicarbonate again slowed the emptying of the resected, achlorhydric stomach.

Our other slides, illustrate the effects of various other meals used. They leave no doubt that the emptying-time

of the resected stomach may be delayed in the same way as that of the normal stomach, not only by acid solutions but by hypertonic solutions of electrolytes or non-electrolytes, fats or any substance capable of adding the proper stimulus to the upper intestinal mucosa. May we thank Dr. Quigley and Dr. Wilson for their discussions; I regret that adequate time is not available to answer the rest of Dr. Wilson's questions.

Dr. Ivy (Chicago): I should like to ask whether there were any observations of the effect of the duodenal tube on gastric emptying: the rate of emptying? That was the first point made by Dr. Wilson.

Dr. Shay: We have now studied more than fifty patients and find that the duodenal tube through the intact pylorus or through the stoma produces no change in gastric emptying.

## ABSTRACTS

PEARSE, H. E., JR.

*Experimental Chronic Intestinal Obstruction From Blind Loops. S. G. and O., Vol. LIX, No. 5, pp. 726-734, Nov., 1934.*

In view of the present day practice of short-circuiting the fecal stream by entero anastomosis above a point of obstruction, the Author set about to study the fate of that inactive segment of bowel between the point of anastomosis and the point of obstruction. Experiments were made on dogs under conditions of surgical anaesthesia and asepsis. The abdomen was opened, and a point twelve inches below the duodeno-jejunal angle determined and marked with a silk stitch. From that point loops of intestine measuring from six inches to six feet were measured in different animals. The distal point was marked and brought beside the proximal one, and an entero-anastomosis made. The loop was obstructed by section and inversion of the ends; the ends were tied together to prevent intussusception. The loop was obstructed in the proximal limb just beyond the anastomosis, at the mid point of the loop or in its distal limb just before the anastomosis giving varying lengths of bowel on both sides of the obstruction. For the sake of comparison in a few animals the loop was created and anastomosed but not obstructed.

It was found that those animals having blind loops distal to the obstruction lived normally in every way and without any disturbance of digestion or nutrition. Peristalsis tends to keep that segment empty. Intussusception of this segment of bowel is apt to occur if it is not guarded against.

When the direction of peristalsis is toward the blind end, material is trapped in it and cannot get out. It was found that such a loop dilated tremendously forming a veritable cesspool. If these loops are less than one foot long, they may empty at intervals and cause no disturbance. Those slightly longer become filled with inspissated material, and if they are not perforated by a foreign body, give rise to mild symptoms of toxæmia. Blind loops over two feet in length become tremendously dilated and hypertrophied, and if perforation does not occur they give rise

to symptoms of chronic intoxication characterized by anorexia, lassitude, weakness, lethargy, emaciation, and finally death. No significant changes were found in the blood non-protein nitrogen, sugar, chlorides, carbon dioxide combining power, sugar or haemoglobin in these animals.

The animals in which the loop was created and anastomosed, but obstructed, showed no symptoms of an intestinal disturbance.

The Author feels that the demonstration of the deleterious effects of blind intestinal loops does not contra-indicate the use of such anastomoses in cases of acute intestinal obstruction when enterostomy is the only alternative procedure. He feels that the avoidance of the messy, often excoriated and painful enterostomy wound, and the necessary subsequent operation, makes entero anastomosis preferable. Such cases should be followed for a long time, and any gastro-intestinal derangements attributable to the blind loop indicate a re-operation.

Two cases are discussed. Four figures and one table accompany the article.

N. M. Percy, Chicago.

ELMAN, ROBERT, M.D., AND ECKERT, C. T., M.D.

*Gastric Acidity as Influenced by Pyloric Closure and Stenosis. Arch. Surg., Vol. 29, No. 6, pp. 1001-1014, Dec., 1934.*

This article is a continuation of experimental work being done at the Washington University School of Medicine on the relation of gastric acidity to the activity of the pyloric sphincter.

These experiments show quite conclusively that pyloric stenosis leads to spontaneous high gastric acidity and interferes with the normal neutralization of acid introduced into the stomach. Closure of the pylorus in the non-anesthetized dog delays or halts while opening re-establishes the normal rapid neutralization of gastric acidity. The Authors feel that these findings add further evidence supporting the idea that duodenal reflex controls in a large part the level of gastric acidity.

These observations show quite conclusively how high gastric acidity can be maintained and suggests that in

turn it may, of itself, initiate inflammatory changes which lead eventually to ulceration, hemorrhage and perforation.

The Authors feel that these experiments add very definite evidence of the relation of acidity to the pathogenesis of peptic ulcer.

N. W. Swinton, Boston.

LESSER, ALBERT, AND GOLDBERGER, H. A.

*The Blood Sedimentation Test and Its Value in the Differential Diagnosis of Acute Appendicitis. S. G. and O., Vol. 60, No. 2, Feb. 1, 1935.*

The Authors using their own modification of the original Westergren technique studied the blood sedimentation test in a variety of clinical conditions. In their study a reaction of from 6 to 15 millimeters in the hour was considered normal, while the reaction of from 80 to 140 millimeters in the hour was considered severe.

In cases of acute full blown pneumonia, regardless of type, the average readings were between 80 and 100 millimeters. As convalescence advanced there was a gradual decrease in that reading; as a complication developed there was a sudden sharp increase in that reading.

In tuberculosis of the lungs the height of the sedimentation reaction was found to be an accurate indication of the extent and activity of the process.

In acute rheumatic fever a high sedimentation reading (from 90 to 100 millimeters) was found during the acute stage, while a lower reading was found as the patients general condition improved. The onset of any complication was marked by a sharp increase in the reaction.

In all cases of acute adnexal disease the reaction was increased, varying from 40 to as high as 150 millimeters. A reading of 20, or less, was found to be absolute assurance of the absence of any acute pelvic infection.

In all cases of acute appendicitis, excepting those with abscess or generalized peritonitis, the reaction was found to be normal, while all other conditions simulating acute appendicitis showed definitely abnormal reactions.

Two tables and a bibliography accompany the article.

N. M. Percy, Chicago.



## SECTION III—*Nutrition*

### Present Conceptions of Calcium Metabolism<sup>\*</sup>

By

DAVID LANDBOROUGH THOMSON  
MONTREAL, CANADA

THE fundamental fact in the chemistry of calcium, which dominates its physiological behaviour, is that some of its commoner salts are highly insoluble. Large quantities of calcium salts, especially complex basic phosphates, are stored in the skeleton in solid form. Sodium and potassium, on the other hand, are present in the body almost wholly in soluble forms; these elements cannot be stored in the tissues unless large amounts of water are stored with them, since otherwise the concentration of the sodium and potassium ions in the tissue fluids would rise above the physiological limits. The metabolism of sodium and potassium is therefore very closely bound up with the metabolism of water: potassium is related to the fluid content of the living cells, and sodium to the external fluids in which the cells are bathed; and the behaviour of potassium and sodium under various circumstances may be taken as an indicator of the behaviour of the intracellular and extracellular water stores, respectively (1). Since calcium, however, can be stored in solid form without the question of concentration of calcium ions arising, its metabolism is not directly connected with the metabolism of water, and is regulated on different principles and by different means and mechanisms.

On the other hand, all recent studies support the view (2) that the stores of calcium in the bones are readily accessible. They may be added to or drawn upon, depending on the physiological circumstances; they do not form an unalterable rigid framework like the steel girders of a concrete building, but rather are to be compared with the stores of glycogen in the liver even if the usual range of fluctuation is not so great. Just as the controlled breakdown of liver glycogen maintains the approximately constant level of the blood sugar during fasting, so the skeletal calcium serves to maintain the serum calcium concentration within normal limits; and just as the formation and breakdown of liver glycogen is largely controlled by insulin and other hormones, so the formation and breakdown of the calcium stores in the bones is largely controlled by the hormone of the parathyroid glands.

The constancy with which the serum calcium is maintained in the neighborhood of 10 mg. per cent in

normal individuals is indeed striking, and becomes still more so when one repeatedly finds this same amount of serum calcium in all the commoner laboratory mammals with the exception of the rabbit. Very striking evidence of the efficiency and accuracy of the regulating processes was supplied by Hastings and Huggins (3). The experiments carried out by these Authors were of the following nature: They removed up to 50 per cent of the whole volume of the circulating blood of a dog and shook it with the highly insoluble salt lead phosphate; this process removed 90 per cent of the calcium present in the blood; the calcium-free blood was then reinjected into the animal. They were able to repeat this procedure again and again upon the same animal, at intervals of only 20 minutes, without greatly lowering the serum calcium content of the successive samples. This indicates that the dog is able to make good sudden loss of 45 per cent of its total serum calcium within 20 minutes, and to do so repeatedly; a very remarkable indication of the lability of the calcium stores in the skeleton.

Until very recent times, all discussions of the importance of the accurate regulation of the serum calcium level have been complicated by the fact that the calcium is present in more than one form. It is well known that if serum be forced through an ultrafilter only a fraction of the calcium passes the membrane. This, and similar experiments, lead to the distinction between diffusible and non-diffusible calcium. Many workers have also considered that even the diffusible fraction may be further subdivided into ionized and un-ionized calcium. Since it is generally considered that only the ionized form is of immediate physiological significance, and since there has not been until recently any convincing account of the equilibrium controlling the various calcium fractions or adequate means of measuring the ionized fraction, it has been difficult to relate determinations of total serum calcium to physiological problems. It has also been supposed that agents which affect calcium metabolism (the parathyroid hormone, for instance) may exert their effects by disturbing the equilibrium between these different forms of calcium. Recently, however, the matter has been convincingly clarified by the brilliant investigations of McLean and Hastings (4). These workers have found sufficiently accurate means of estimating the concentration of calcium ions in serum or other fluids by biological assay, using the

\*McGill University, Montreal.

Read at the 38th Annual Session of the American Gastro-Enterological Association, Atlantic City, N. J., June 10-11, 1935.

Approved by the Publications' Committee of the Association.



isolated frog heart as a test object, and the results of this study indicate that in most cases we need take account of only two forms of calcium in the serum—free calcium ions and calcium bound to the serum proteins. The equilibrium connecting these two fractions is a reversible one governed by simple chemical laws (the law of mass action in particular), and from our knowledge of this equilibrium it is possible accurately to predict the concentration of ionized calcium if the total calcium concentration and the serum protein concentration are known.

With a normal serum calcium of 10 mg. per cent and 7 per cent total serum protein, approximately two-fifths of the calcium is in the free ionized state. If the serum be simply diluted with calcium-free saline, the ionized calcium is not so greatly reduced as the total calcium: that is to say, proteins liberate some of the bound calcium. If the total calcium concentration of the serum falls while the serum protein remains unaffected, the decrease in ionized calcium is relatively greater than the decrease in total calcium, though not very strikingly so. If the serum protein concentration falls while the total calcium remains constant, the fraction of the calcium which is ionized will naturally be increased. The ratio between free and bound calcium is only slightly affected by changes in the albumin-globulin ratio or in the hydrogen ion concentration, and is not directly controlled by the amount of parathyroid hormone or by any other of the agents known to intervene in calcium metabolism. These studies have eliminated from discussion numerous theories of calcium metabolism which invoked shifts in the equilibrium between the different forms of calcium and which, though difficult to disprove, were not helpful to an understanding of the fundamental problems involved.

We may turn now to discuss some of the physiological properties of the ionized calcium on which the therapeutic use of calcium salts largely depends. In the first place there is a certain sedative action, both peripheral and central, which has led to the use of calcium in such spastic states as those produced by spider bites. We have been accustomed to think rather of the sedative effect of magnesium salts administered intravenously, and to think of the sedative or even narcotic effect of calcium salts in a rather negative manner, since the neuromuscular irritability caused by decrease in the serum calcium is more striking and has been more studied than its converse. Moreover, calcium tends to inhibit magnesium narcosis. In recent years, however, irritability due to deficiency of magnesium has become familiar (5, 6), and on the other hand we are beginning to recognize the sedative effects of increased calcium ion concentration. My colleagues, Drs. Andreyev and Pugsley (7), have used the conditioned reflex method to study the effects of maintenance of the serum calcium at a high level by continued administration of parathyroid hormone or irradiated ergosterol, and have shown that dogs so treated display an enhancement of all inhibitory processes; they have thus given objective and quantitative expression to the not unfamiliar idea that animals subjected to such treatment are drowsy and apathetic. Others have shown (8) that calcium salts administered intravenously have a sedative action upon intestinal colic, especially the colic of acute lead poisoning. There can be no doubt of the efficacy of this mode of treatment although it has not been possible to sup-

port it in animal experimentation (9). The pains are so rapidly allayed that the effect cannot be due simply to removal of lead from the circulation, although as is well known the metabolism of lead is very similar to that of calcium and it is possible to cause lead to be deposited out of harm's way in the bones by creating circumstances leading to deposition of calcium. Whether the alleged therapeutic value of calcium in ulcerative colitis (10) and tuberculous enteritis should be considered under this heading or not is uncertain.

Calcium salts have also found therapeutic application in the treatment of allergic manifestations, especially bronchial asthma (11), although uniformly successful results are not always obtained. It is probable that this action of calcium is not to be linked with its sedative effect, but rather with a somewhat vague and elusive relation which appears to exist between calcium and the sympathetic nervous system; that is to say, the action of the calcium on the bronchial musculature may be regarded as analogous to the action of adrenalin or ephedrine. This relation between calcium and the sympathetic nervous system has recently been analyzed (12) but appears to be extremely complex and is not in all cases to be depended upon.

One important property of calcium salts, which falls under a different heading since it does not depend upon calcium ion concentration, is the acidifying action. If calcium chloride is given by mouth the calcium is less completely absorbed than the chloride, and partly remains in the intestine as calcium phosphate or carbonate. This tends to reduce the bicarbonate ion concentration of the blood and thereby to produce a relative alkali deficiency (13). In some circumstances the acidosis so obtained may have therapeutic value, since acidosis has in itself sedative effects—hence, for instance the use of the ketogenic diet in the treatment of epilepsy.

The control of calcium metabolism exerted by the parathyroid hormone has already been referred to and is of course very familiar. In the doses commonly employed the parathyroid hormone elevates the serum calcium by withdrawing calcium from the skeleton. The elevation is transient though longer than that obtainable by intravenous injection of calcium salts. Attention may be called at this time to the fact that the unit in which the dosage is most commonly expressed has now been discarded. The most widely used commercial preparations are biologically assayed on dogs, and the results have hitherto been expressed in the units originally defined by Collip (14). One hundred of these units is the amount required to elevate the serum calcium of normal dogs weighing 20 kilograms by 5 mg. per cent in 12 to 15 hours. It has now been decided that the unit proposed by Hanson has priority over the Collip unit. The Hanson unit was supposed to be determined on parathyroidectomized dogs and is a much smaller quantity than the Collip unit. Extracts which have hitherto been described as containing 20 Collip units per cubic centimeter are now described as containing 100 Hanson units in the same volume, although the extract itself is unchanged. It is to be feared that some confusion will result until the new dosage becomes familiar.

Several theories of the mode of action of the parathyroid hormone have been proposed. It has been suggested, for instance, that the parathyroid hormone lowers the renal threshold to phosphates, and that the

resultant fall in plasma phosphate concentration allows the plasma to hold larger quantities of calcium in solution. Against this theory may be cited the fact (15) that the characteristic histological changes produced in the bones by the administration of parathyroid extract are obtainable in nephrectomized animals. It has already been observed that the work of McLean and Hastings permits us to dismiss a number of theories of parathyroid hormone action. A survey of the available evidence (16) has led my colleagues and me to the conclusion that the action of the parathyroid hormone is best explained as a direct stimulus to the living cells of the bone. Moderate or large doses lead to the appearance of great numbers of osteoclasts, whose function it is to break down bone; but, if such doses are continued or if small doses are initially applied, elevation of the serum calcium is not observed and histological examination of the bones shows proliferation of osteoblasts which are concerned with the process of apposition (17).

Other agents which lead to release of calcium from the skeleton do not involve the osteoclastic reaction. This applies, for example, to the effect of all types of acidosis, to the effect of very large doses of irradiated ergosterol and to the effect of experimental or clinical hyperthyroidism. There is no explanation at present for the fact that, while both thyroid and parathyroid hormones lead to excretion of calcium removed from the skeleton, the former fails to produce hypercalcaemia and the calcium is excreted chiefly in the faeces. Yet the thyroid hormone appears to be no less efficient than the parathyroid hormone in liberating calcium from the skeleton and there is evidence (18) that the effect is a specific one; it does not appear to be due merely to the general elevation of metabolism, since it is not observed in the elevated metabolism of subacute endocarditis. On the other hand, my colleague, Dr. Pugsley (19), has shown that the metabolic stimulant dinitrophenol, leads, like the thyroid hormone, to a marked increase in the faecal excretion of calcium in the rat.

#### REFERENCES

- Gamble, J. L., Ross, S. G., and Tisdall, F. F.: The metabolism of fixed base during fasting. *J. Biol. Chem.*, 57:633, 1923.
- Bauer, W., Aub, J. C., and Albright, F.: A study of the bone trabeculae as a readily available reserve supply of calcium. *J. Exp. Med.*, 49:145, 1929.
- Hastings, A. B., and Huggins, C. B.: Experimental hypocalcemia. *Proc. Soc. Exper. Biol. and Med.*, 30:458, 1933.
- McLennan, F. C., and Hastings, A. B.: The state of calcium in the fluids of the body. *J. Biol. Chem.*, 108:285, 1935.
- Kruse, H. D., Orent, E. R., and McCollum, E. V.: Studies on magnesium deficiency in animals. *J. Biol. Chem.*, 100:603, 1933.
- Hirschfelder, A. D., and Hurry, V. G.: Clinical manifestations of high and low plasma magnesium. *J. A. M. A.*, 102:1138, 1934.
- Andreyev, L., and Pugsley, L. I.: A study of the effects of hypercalcaemia upon the activity of the cerebral cortex. *Quart. J. Exp. Physiol.*, 24:189, 1934.
- Bauer, W., Salter, W. T., and Aub, J. C.: The use of calcium chloride to relieve peristaltic pain. *J. A. M. A.*, 96:1216, 1931.
- Fitzhugh, G., Miller, M. L., Taylor, G. W., and Aub, J. C.: The effect of intravenous calcium chloride on peristalsis following intestinal obstruction in dogs. *Amer. J. Physiol.*, 97:142, 1931.
- Haskell, B., and Cantarow, A.: Calcium and parathyroid therapy in chronic ulcerative colitis. *Amer. J. Med. Sci.*, 181:180, 1931.
- Cantarow, A.: "Calcium Metabolism and Calcium Therapy." Philadelphia, Pa. (Lea and Febiger), p. 173, 1931.
- Baer, Z. M., and Rosenblueth, A.: The action of calcium and potassium ions on the rictating membrane, the adrenal medulla, and the non-pregnant uterus of the cat. *Amer. J. Physiol.*, 108:46, 1934.
- Gamble, J. L., Blackfan, K. D., and Hamilton, B.: A study of the diuretic action of acid-producing salts. *J. Clin. Invest.*, 1:359, 1925.
- Collip, J. B., and Clark, E. P.: Further studies on the physiological action of a parathyroid hormone. *J. Biol. Chem.*, 64:455, 1925.
- Collip, J. B., Pugsley, L. I., Selye, H., and Thomson, D. L.: Observations concerning the mechanism of parathyroid hormone action. *Brit. J. Exper. Path.*, 15:335, 1934.
- Thomson, D. L., and Collip, J. B.: The parathyroid glands. *Physiol. Rev.*, 12:309, 1932.
- Pugsley, L. I., and Selye, H.: The histological changes in the bone responsible for the action of parathyroid hormone on the calcium metabolism of the rat. *J. Physiol.*, 79:113, 1933.
- Aub, J. C., Bauer, W., Heath, C., and Ropes, M.: Studies on calcium and phosphorus metabolism: the effect of thyroid hormone and thyroid disease. *J. Clin. Invest.*, 7:97, 1929.
- Pugsley, L. I.: The effect of 2:4-dinitrophenol upon calcium, creatine and creatinine excretion in the rat. *Biochem. J.*, 29:2247, 1935.

#### DISCUSSION:

DR. A. C. IVY (Chicago, Ill.): Dr. Thomson in my opinion is to be commended for presenting a very concise abstract of our present knowledge of the physiologic aspects of calcium metabolism. It is a type of paper which does not lend itself to discussion.

About all that a discussant can do is to pick out certain points or facts that have been mentioned, and call upon his own experience for purposes of emphasis.

One point that I have in mind and which I think deserves emphasis is the importance of the reaction of the contents of the gastro-intestinal tract on the absorption of calcium. We all know that calcium is absorbed better when we have an acid reaction in the upper intestine; however, it was not until recently that I realized the importance of the secretion of hydrochloric acid in this regard.

Last year and about this time I removed the stomachs from four puppies about six weeks old. We kept them on a special diet that contained adequate quantities of calcium for growing puppies, more than 2 grams a day. About six months later two of these puppies became bowlegged.

X-ray pictures were taken which showed marked undercalcification of the bones of the body in all four puppies, and there was undercalcification to such an extent in two of them that bowleggedness had occurred.

Vitamin D was not concerned, because these puppies had been given daily tablespoonful doses of cod liver oil. That caused us to make X-ray photographs of our adult gastrectomized dogs, or dogs that had been gastrectomized when they were adults. We found that they had less calcium in their bones than dogs which had been kept in our colony about the same length of time, on the same diet.

This observation shows the importance of the secretion of hydrochloric acid for the absorption of calcium from the upper intestine and that the secretion of acid is more important, in infancy and childhood where large quantities of calcium are necessary, than in the adult where a large quantity of calcium is not necessary, because growth has occurred.

Dr. Thomson referred to the use of calcium in the relief of various types of visceral colics. Dr. Quigley and I, several years ago, and others in my laboratory on different occasions, have injected calcium intravenously to see its effect upon hunger contractions. Either it has no effect or only temporarily inhibits hunger contractions. I think Dr. Thomson is correct when he says that we do not know why calcium intravenously relieves biliary colic or colon colic. We can look upon it only as a "corrective." We have at present to view the therapeutic use of calcium in a number of conditions as a type of corrective. For example, the use of calcium in the bleeding tendency of jaundice—we don't know how the calcium works; yet we know there are some instances in which it works.

We have found that Vitamin D has a favorable influence on the hemorrhagic tendency in jaundice. It doesn't affect the calcium in the blood, but it does decrease the bleeding-time in the presence of jaundice. Since we do not know how it works, we can only say that it has a corrective action.

DR. LAY MARTIN (Baltimore, Md.): Dr. Ivy has well said that this paper does not lend itself to discussion. There is very little left to be said, particularly after Dr. Ivy has talked. There are a few related topics, however, that I should like to mention.

Dr. Thomson pays just tribute to the excellently conceived and completed investigations of McLean and Hastings. There is no doubt that their work is of tremendous importance, and, if their frog's heart method for the determination of ionized calcium is definitely applicable to human serum at its higher temperature, they have done a great deal to advance our ability to study this complex problem, "calcium metabolism."

It is simple to understand the algebraic approach to their formula for the determination of ionized calcium in relation to the law of "mass action." From the geometrical approach, however, it is not so easy. Suppose we take the two states of hypoparathyroidism and hyperparathyroidism: in the former we find a normal content of serum proteins, and according to their formula, a decreased amount of  $\text{Ca}^{++}$ ; in the latter condition, hyperparathyroidism, we find high ionized calcium, and a normal amount of serum protein. Is it not possible that there may be changes in the calcium affinity of the serum proteins in the two conditions?

Intimately connected with calcium metabolism is the condition known as tetany. In states of hypoparathyroidism (based on either disease processes or operative interference), and calcium low rickets, it has long been known that tetany will ensue when calcium decreases below a certain level. However, tetany is frequently seen in conditions in which serum calcium is found to be within normal limits, as examples of such states are protracted loss of gastric juice, and hyperpnea, either of which will produce an alkalosis.

In the former conditions, paliative relief may be at times obtained by calcium or ammonium chloride or  $\text{HCl}$ , in fact anything that will produce an acidosis. To permanently cure these types of tetany, measures must be made to raise the level of calcium serum in hypoparathyroidism by parathyroid hormone, and in calcium low rickets by readjustment of intestinal calcium absorptive ability, viz., Vitamin D or heliotherapy and increase in the acidity of intestinal contents.

The tetany that is found in instances of chloride or  $\text{CO}_2$  loss is best regulated by any chemical that will counteract the alkalosis. Calcium or ammonium chloride act in this manner.

In connection with the therapeutic usage of calcium chloride in cases of bronchial asthma, I would like to ask Dr. Thomson if he does not feel that its beneficial result is due more to its dehydrating effects than to the direct

action of the calcium ion. The similar effects obtained after injections of parathormone would seem to be indicative of this. Furthermore, may this not also apply to its helpful action in intestinal colic?

One more word on the mode of action of parathormone. The idea of increased osteoclastic action causing dimineralization does not seem to me acceptable especially as Dr. Thomson has already stated it is not seen in cases of dimineralization with associated acidosis, hyperthyroidism, and osteoporosis. It would seem that some marked disturbance of total serum ions as evidenced by their increase in the urine might be a more satisfactory basis.

DR. DAVID L. THOMSON (closing the discussion): There really remains very little for me to say except to thank Dr. Ivy and Dr. Lay Martin for their courtesy in discussing the paper which, as they both said, and as I firmly realize, does not lend itself to discussion in any way, and, as far as the questions raised by Dr. Martin are concerned, I think I can justifiably excuse myself from defenses of other people whose papers I have merely abstracted for your benefit.

In regard to the last point, that is one in which I have been interested myself. On account of lack of time I omitted a small section of the paper which dealt with that and I should like to make one comment upon it.

One popular view of the mode of action of parathormone has been that it affects the renal threshold for phosphates. There apparently is rapid increase in the rate of phosphate excretion immediately after the injection of the parathyroid hormone, and it has been suggested this leads to a fall of plasma phosphate which permits a corresponding rise in serum calcium.

I have been unable to subscribe to this view, for various reasons. First, that we have been able to show that a rise in serum calcium produced by parathormone is not necessarily preceded or accompanied by any decrease in total serum phosphate, or in the particular trivalent phosphate ion species which is presumably concerned in this equilibrium. Second, and perhaps more conclusive, is that we have been able to show that the characteristic histologic changes produced in the bone, the appearance of osteoclasts, is obtainable in the nephrectomized animal; and, therefore, whatever influence the parathyroid hormone has upon the immediate excretion of phosphate (and I don't doubt it has one, though I have not studied the question myself), I do not feel that is the cause of the subsequent and more conspicuous rise in the serum calcium.

## ABSTRACTS

GRAHAM, E. A., M.D., F.A.C.S., AND  
HARTMAN, A. F., M.D.

"Subtotal Resection of the Pancreas for Hypoglycemia." *S. G. and O.*, Vol. 59, No. 3, Sept., 1934.

In this article, the Authors report the case of a child, one year old, in which eighty to ninety per cent of apparently normal pancreatic tissue was removed for hypoglycemia with an excellent result at the end of nine months.

At the Barnes Hospital, a total of five successful cases of adenoma of the islet tissue of the pancreas for hypoglycemia have now been operated and several more have been reported by other surgeons. However, in the cases of hypoglycemia where normal pancreatic tissue has been found and less than two-thirds of the pancreas has

been removed, the results have not been entirely satisfactory. They call attention to the analogy which has been so often made between hyper-insulinism and hypoglycemia and hyperthyroidism and call attention to the fact that the end results in the surgery of the thyroid in patients with hyperthyroidism were not successful until radical subtotal removals of the thyroid gland were done.

The case reported will not be repeated in detail in this abstract. It was a child of one year who had had repeated convulsions and a marked retardation in mental development. Following the removal of eighty to ninety per cent of the pancreas, only a small remnant of pancreatic tissue being left to protect the common bile duct, the

blood sugar, although it first raised to an abnormally high level, later became practically normal in amount. All of the symptoms caused by the hypoglycemia promptly disappeared and had not recurred at the end of nine months. The mental and physical states of the patient showed marked improvement.

Microscopic study showed the removed tissue to be essentially normal. Although the Authors felt that the other known causes of hypoglycemia had apparently been satisfactorily excluded, they could not definitely state whether this case was due to hypo-insulinism or to some other factor.

This case is unique in that it is the youngest case reported and also larger portions of the pancreas were removed than have been previously done.

N. W. Swinton, Boston.

## SECTION IV—Roentgenology

### The Role of Vitamin B<sub>1</sub> in Tonus of the Large Intestine \*

By

M. I. SPARKS, M.D.

and

E. N. COLLINS, M.D.

CLEVELAND, OHIO

THE importance of the relationship between the tonicity of the colon and a diet deficient in vitamins and particularly one deficient in vitamin B<sub>1</sub> has received increasing clinical attention since the original experiments of McCarrison. The factors which are involved in the maintenance of tonicity of the colon are related not only to the function and disease of this organ *per se*, but also to those more generalized conditions in which improper action of the bowels seems to play a most important part.

Since the advent of roentgenology, it is well known that the incidence of atonicity of the colon is high. This has been ascribed to diverse causes, such as congenital abnormalities, constitutional states, the debility accompanying various "disease states," local mechanical factors or to pure neuroses. The present work was undertaken as a preliminary study in the investigation of one of these generalized conditions, and while the importance of factors mentioned above is realized, we wish to add evidence which appears to indicate that a deficiency in vitamin B<sub>1</sub> may be an accompanying factor, if not the important factor in the production of abnormal conditions of colon tonus.

In this work, roentgen studies including both fluoroscopic and film examinations, as well as volume-capacity determinations of the colon, were made on adult rats which were fed diets deficient in vitamin B<sub>1</sub>. The opaque medium used was a 10 per cent solution of sodium iodide and this was administered as an enema. In a period of seven months, more than 250 enemata were given to 80 rats.

Hargreaves, Fletcher, and Dickson (1) measured the volumes of colons of young rats before and after diets which were deficient in vitamin B<sub>1</sub> had been fed. They found that about two months after the deficiency diet was initiated, the colons definitely were increased in size and volume-capacity. They believed that vitamin B<sub>1</sub> was the most important factor in the production of this change, but that excess of carbohydrate and absence of vitamin B<sub>2</sub> accentuated the atonic changes. Harris and Bunker (2) have shown that vitamin D plays a part in maintaining normal motility

of the gastro-intestinal tract, but they do not mention specifically any effect on the tonus of the colon.

In our experiments, in addition to the larger group of adult rats which were fed a diet deficient in vitamin B<sub>1</sub>, a control group was examined. These two groups of animals were maintained on similar diets except for the deficiency in vitamin B<sub>1</sub> in the food of the experimental group. After atonicity of the colons had developed, Hargreaves, Fletcher, and Dickson (1), added vitamin B<sub>1</sub> to the diet of their animals and this resulted in a disappearance of the atonicity. In our experiments, it was desirable to use the rats for other purposes as soon as atonicity of the colon was demonstrated, so the effect of the relief of atonicity by the addition of vitamin B<sub>1</sub> in the diet has not been observed. However, we believe that the results of our study of the control group overcome this discrepancy, at least in part.

#### METHOD

*Diets.* Two different diets were used in feeding two separate groups of adult rats.

Diet 1.—This was the synthetic diet described by Chase and Sherman (3) and deficient only in vitamin B<sub>1</sub>.

Diet 2.—This was a complete synthetic diet in the same proportions as Diet 1. The yeast was not autoclaved and thus both vitamins B<sub>1</sub> and B<sub>2</sub> were retained.

*Enemata.* When we first worked out the method, one or more preliminary cleansing enemata were given, but this procedure soon was discarded because it was found that the results were more satisfactory and more consistent when no preparation was administered.

The rats were fastened in the supine position, a large cannula was inserted into the rectum and secured there by a tight ligature which surrounded the tail and the skin just cephalad to the anus. In our experience, if the enema is to be retained, correct application of this ligature is essential. If any seepage occurred during the experiment, the result was discarded.

The opaque fluid (10 per cent sodium iodide) was introduced from a 50 c.c. burette, in which the level of the fluid at the beginning of every enema was the same. This assured a fairly constant hydrostatic pressure for each enema. The top of the fluid level was approximately 45 cm. from the top of the table.

The fluid was allowed to run in slowly until it reached the ileo-cecal region, when the flow was stopped and the reading taken. The entire flow into the colon was followed

\*From the Cleveland Clinic.  
Submitted October 10, 1935.

under the fluoroscope and, as soon as the colon was filled, an attempt was made to secure a roentgenogram. This, however, was rather difficult to obtain because in the rat, there is little or no valve action at the ileocecal junction. This resulted in a very quick regurgitation of the fluid

less, there is considerable individual variation. We had expected to find considerable divergence and it has been surprising to find that the values on the same rat which had been fed Diet 2 have checked very

TABLE I  
*Volumes of Colons of Rats Fed on Diet 1*

| Rat No. | Date     | Weight | Volume of Colon in c.c. | Date    | Weight | Volume of Colon in c.c. | Date    | Weight | Volume of Colon in c.c. | Date    | Weight | Volume of Colon in c.c. | Per cent of Change in Colon-Volume at End of from 2 to 3 months |
|---------|----------|--------|-------------------------|---------|--------|-------------------------|---------|--------|-------------------------|---------|--------|-------------------------|-----------------------------------------------------------------|
| 1       | 3-21-35  | 254    | 6.2                     | 4-30-35 | 277    | 5.8                     |         |        |                         |         |        |                         | -6                                                              |
| 4       | 12-11-34 | 303    | 3.6                     | 3-21-35 | 232    | 7.5                     | 5-2-34  | 252    | 7.6                     |         |        |                         | +108                                                            |
| 5A      | 12-4-34  | 254    | 7.2                     | 2-7-35  | 239    | 8.8                     |         |        |                         |         |        |                         | +22                                                             |
| 6       | 12-11-34 | 152    | 3.8                     | 2-7-35  | 182    | 4.8                     | 3-21-35 | 188    | 4.6                     |         |        |                         | +26                                                             |
| 7A      | 12-11-34 | 109    | 2.0                     | 2-7-35  | 141    | 7.2                     |         |        |                         |         |        |                         | +260                                                            |
| 7B      | 3-21-35  | 174    | 3.0                     | 5-2-35  | 178    | 3.5                     |         |        |                         |         |        |                         | +17                                                             |
| 8B      | 12-21-34 | 148    | 3.3                     | 2-7-35  | 204    | 6.9                     | 5-2-35  | 239    | 5.4                     | 6-13-35 | 251    | 4.9                     | +109                                                            |
| 11B     | 3-14-35  | 172    | 5.3                     | 4-30-35 | 191    | 3.0                     |         |        |                         |         |        |                         | -43*                                                            |
| 12      | 12-11-34 | 162    | 2.0                     | 2-7-35  | 208    | 5.8                     | 5-2-35  | 200    | 5.2                     | 6-13-35 | 200    | 4.3                     | +190                                                            |
| 13A     | 12-21-34 | 119    | 3.7                     | 2-7-35  | 134    | 3.7                     |         |        |                         |         |        |                         | +0                                                              |
| 16A     | 12-4-34  | 182    | 3.0                     | 2-7-35  | 191    | 6.3                     |         |        |                         |         |        |                         | +110                                                            |
| 16B     | 4-9-35   | 245    | 2.4                     | 6-13-35 | 261    | 4.9                     | 7-11-35 | 261    | 2.2                     |         |        |                         | +104                                                            |
| 18      | 12-4-34  | 190    | 6.4                     | 2-7-35  | 182    | 4.6                     | 3-21-35 | 180    | 4.0                     | 5-2-35  | 175    | 4.0                     | -28                                                             |
| 20B     | 5-9-35   | 265    | 4.0                     | 6-13-35 | 302    | 6.2                     | 7-11-35 | 310    | 7.0                     |         |        |                         | +75                                                             |
| 22B     | 5-11-35  | 250    | 3.0                     | 6-20-35 | 297    | 7.6                     |         |        |                         |         |        |                         | +153                                                            |
| 23B     | 4-4-35   | 200    | 2.8                     | 4-11-35 | 200    | 2.7                     | 5-28-35 | 234    | 4.1                     | 6-20-35 | 247    | 5.0                     | +80                                                             |
| 23      | 12-11-34 | 137    | 3.9                     | 2-7-35  | 140    | 3.1                     | 5-2-35  | 169    | 3.0                     |         |        |                         | -23                                                             |

70 per cent increased in volume. Average increase 104 per cent.

30 per cent unchanged or decreased in volume. Average change, -20 per cent.

\* Only 1 month.

into the small bowel, and thus good roentgenograms of the colon were obtained in only a small percentage of the cases.

In a few cases, the enemata were repeated at short intervals to check the accuracy and constancy of the results. Usually, however, one opaque enema was given before the diet was started and a second one after the animal had been on the diet for approximately two months. Hargreaves, Fletcher, and Dickson (1) found the maximum effect to have occurred at this time and our results agree with their observations.

## RESULTS

By the use of the technique described above, the normal volume of the colon in an adult rat which

closely when the enemata have been repeated within a few days or even a few weeks.

The method, nevertheless, is a rough one and does not permit fine measurements. But even with this difficulty, we believe the results are sufficiently striking to show the effect of diet on colonic tonus. This definite change is shown in Figure 1 which exhibits the appearance of the colon before the deficiency diet was begun, and in Figure 2 which demonstrates the appearance two months later.

We secured the following results, which may also be noted in the Tables: In the group which received a diet deficient in vitamin B<sub>1</sub>, the volume of the colon was increased in 70 per cent of the animals, while in

TABLE II  
*Volumes of Colons of Rats Fed on Diet 2*

| Rat No. | Date    | Weight | Volume of Colon in c.c. | Date    | Weight | Volume of Colon in c.c. | Date    | Weight | Volume of Colon in c.c. | Per cent of Change in Colon-Volume at End of from 2 to 3 months |
|---------|---------|--------|-------------------------|---------|--------|-------------------------|---------|--------|-------------------------|-----------------------------------------------------------------|
| 21C     | 4-30-35 | 237    | 4.9                     | 6-20-35 | 250    | 3.8                     |         |        |                         | -22                                                             |
| 26A     | 4-30-35 | 192    | 4.0                     | 6-20-35 | 245    | 4.0                     |         |        |                         | +0                                                              |
| 27      | 4-30-35 | 208    | 3.4                     | 6-20-35 | 289    | 3.0                     |         |        |                         | -12                                                             |
| 28C     | 4-30-35 | 293    | 3.9                     | 7-11-35 | 348    | 3.4                     |         |        |                         | -13                                                             |
| 29      | 4-4-35  | 206    | 5.2                     | 4-30-35 | 217    | 6.7                     | 6-13-35 | 210    | 4.0                     | -23                                                             |
| 30      | 4-11-35 | 204    | 3.0                     | 6-13-35 | 191    | 2.7                     |         |        |                         | -10                                                             |
| 31      | 4-4-35  | 183    | 4.0                     | 5-28-35 | 219    | 3.2                     | 6-20-35 | 243    | 4.9                     | 2nd month +22                                                   |
| 32      | 4-4-35  | 199    | 3.0                     | 5-11-35 | 198    | 3.3                     | 5-28-35 | 193    | 4.9                     | 2nd month +63                                                   |
| 33B     | 4-4-35  | 193    | 4.9                     | 5-11-35 | 189    | 2.3                     |         |        |                         | -53                                                             |

77 per cent unchanged or decreased in volume. Average change, -19 per cent.

23 per cent increased in volume. Average increase 42 per cent.

weighs from 200 to 300 gms. is between 3.0 c.c. and 4.5 c.c. There seems to be no definite relationship between the weight of the animal and the size of the colon, even though the larger adult rats tend to have larger colons than the smaller adult rats. Neverthe-

30 per cent there was no change or there was a decrease in size. The striking feature was the amount of change which was found in each individual rat, if any increase in the size of the colon was noted. In most of these rats, the size of the colon was doubled.



Fig. 1. Roentgen appearance of colon before deficiency diet was begun.

Of those rats in which an increase in colon volume was shown, the average increase was 104 per cent. On the other hand, in the remaining rats in which no change or a decrease in volume was shown, the average decrease was only 20 per cent.

In the group which received the complete synthetic diet (Diet 2), the volume-capacity of the colon remained unchanged or decreased in 77 per cent, while in the remaining 23 per cent it was increased. Furthermore, the amount of change in each individual rat was much less than was found in those fed the diet deficient in vitamin B<sub>1</sub> (Diet 1). The average decrease in size was only 19 per cent, while in those in which the colon became larger, there was an average increase of 42 per cent.

Thus, the colons of rats maintained on a diet deficient in vitamin B<sub>1</sub> increase in size for a period of from two to three months. If the deficiency diet is continued longer than this, there is some evidence to suggest that a decrease in size takes place, although the original size has not been regained during the period of our observation. However, our results in this regard are not conclusive.

#### SUMMARY

1. By use of the technique described, it was found that the normal volume of the colon of adult rats is from 3.0 c.c. to 4.5 c.c.

2. The volume of the colons of rats maintained on a diet deficient in vitamin B<sub>1</sub> for two months increased strikingly in 70 per cent of the animals.

3. No such change occurred in a control group maintained on a complete synthetic diet.



Fig. 2. Roentgen appearance of colon two months after deficiency diet was begun.

#### REFERENCES

1. Hargreaves, Florence, Fletcher, A. A., and Dickson, W. H.: Influence of diet on motor and trophic functions of colon in rats. *Tr. Roy. Soc. Canada*, 25:197-198, May, 1931.
2. Harris, R. S., and Bunker, J. W. M.: Roentgenographic study of gastro-intestinal motility in rachitic rats. *Am. J. Roentgenol.*, 33:25-30, January, 1935.
3. Chase, E. F., and Sherman, H. C.: A quantitative study of determination of antineuritic vitamin B. *J. Am. Chem. Soc.*, 53:3506-3510, 1931.



## SECTION V—*Therapeutics*

### Colon Bacillus Vaccine Therapy<sup>\*</sup>

As Related to Chronic Functional Diarrhea, Chronic Headache, Chronic "Toxic Vertigo"  
and "Unstable" Colon (Non-Ulcerative Colitis).

By

JOHN G. MATEER, M.D., JAMES I. BALTZ, M.D.,  
JAMES FITZGERALD, M.D.

and

HARRIS L. WOODBURN, M.D.†  
DETROIT, MICHIGAN

#### INTRODUCTION

THE observations and conclusions outlined below supplement those presented by the same Authors in an earlier publication (1). In it the Authors' initial experience with autogenous polyvalent stool vaccine therapy was reported. During the subsequent four years it has been possible, without sacrificing therapeutic effectiveness, to simplify this method of therapy, and render it more practical, by using stock colon bacillus vaccine. Furthermore, a more extensive experience with this type of vaccine-therapy has contributed more exact knowledge, as to the indications and contra-indications for its use and regarding its limitations.

In the previously reported experience with autogenous, polyvalent stool-vaccines, 100 per cent of the 68 cases, with chronic irritable colon and associated symptoms, exhibited skin sensitivity to *B. coli* vaccine, viz., either to *B. coli communis* or *communior*. Positive skin reactions to *B. coli communis* occurred in 95% of the cases, and to *B. coli communior* in 96%. The skin reactions to both strains were marked, the average diameter being 4.5 cm. Positive skin reactions to other stool bacteria were less constantly present and less marked. Similar skin tests were carried out upon a group of normal individuals. In this control group, positive skin reactions to *B. coli communis* occurred in 65% of the cases, to *B. coli communior* in 69%, and to other stool organisms in a smaller percentage of cases. In the control group slightly more than 90% of the cases yielded a positive skin reaction to either one strain or the other of the colon bacillus. The average degree of skin sensitivity to *B. coli* vaccine in the normal control group was somewhat less than in the "irritable" colon group.

This original group of 68 *obstinate* cases of irritable colon, whose symptoms persisted after the usual

comprehensive therapy, were treated then with polyvalent autogenous stool vaccines. Each vaccine included those organisms to which the patient was skin sensitive. Definite and gratifying improvement was noted, in the majority of instances, in the following symptoms, viz., colon pain, associated pylorospasm distress, constipation, and associated headache and vertigo. It was apparent, therefore, that this type of vaccine therapy constituted a valuable supplementary therapeutic measure.

#### SIMPLIFICATION OF VACCINE METHOD

The preparation of autogenous, polyvalent stool vaccines, of various dilutions for each patient, involved considerable expense and loss of time. For several reasons, it was suspected that similar favorable vaccine effects might be produced by administering *B. coli* vaccine alone. This hypothesis was tested by treating a group of cases with colon bacillus vaccine. A stock vaccine was employed, including the two strains of *B. coli*. The therapeutic results obtained have been essentially similar to those previously resulting from autogenous polyvalent stool vaccines. The treatment of a larger and more varied group of cases, however, has added much additional knowledge relating to this subject.

#### SKIN TESTS

During the interval of four years since autogenous stool vaccines were discontinued, the preliminary skin tests have been continued, but with individual stock vaccines of the three commonest stool organisms to which these cases are skin sensitive, viz: the colon bacillus, staphylococcus aureus and streptococcus fecalis. These skin tests could be omitted, but there have been three advantages in continuing them. In the first place, the degree of local skin sensitivity, and, in some cases, systemic reaction, have been evaluated. This information has been of help in determining the subsequent optimum dosage. In the second place, the

<sup>\*</sup>Read at the 38th Annual Session of the American Gastro-Enterological Association, Atlantic City, N. J., June 10-11, 1935.

Approved by the Publications' Committee of the Association.

†From the Gastro-Intestinal Division of the Medical Department, Henry Ford Hospital.

initial intradermal injection apparently has had a desirable desensitizing effect. Finally, in the occasional cases in which there is a *marked* reaction to streptococcus fecalis or staphylococcus aureus vaccine, this information is obtained; and either or both of these stock vaccines can be added, if desired, to the *B. coli* vaccine for subsequent therapy. However, in the much larger group of cases, showing only slight to moderate skin reaction to the other organisms, *B. coli* vaccine alone has been used routinely.

In a large group of 3,000 cases, with "unstable" colon and the related conditions referred to below, skin tests have been conducted with the three stock vaccines listed above. A one billion concentration of each vaccine has been used for the skin tests. In those patients whose tolerance to the vaccine has been questionable, the skin tests have been omitted entirely, to avoid any undesirable, temporary reactions, due to the initial use of a concentrated vaccine. The results are summarized in Table 1. In addition to the tabulated

TABLE I

*Skin Sensitivity to Stock Stool Vaccines in 3,000 Cases of Related Functional Conditions\* (One Billion Organisms per c.c. of Vaccine)*

| Vaccine Used                 | Cases with + Skin Reaction | Average Di meter of Skin Reaction |
|------------------------------|----------------------------|-----------------------------------|
| <i>B. Coli</i>               | 99%                        | 4.0 x 3.9 cm.                     |
| <i>Staphylococcus Aureus</i> | 45%                        | 2.2 x 2.3 cm.                     |
| <i>Streptococcus Fecalis</i> | 42%                        | 1.6 x 1.7 cm.                     |

\*Unstable colon, toxic vertigo, chronic headache, and functional diarrhea.

local skin reactions, there was some systemic reaction in 25% of the cases, e.g., transient malaise, fatigue or other evidence. Recently more dilute concentrations of vaccine have been used in conducting the skin tests.

#### MECHANISM INVOLVED IN *B. COLI* VACCINE THERAPY

Where vaccine therapy is used with good therapeutic effect, and the vaccine utilized has produced a positive skin reaction prior to treatment, the speculative question might be raised as to whether the results are produced by an actual allergic mechanism or a non-specific protein reaction. The purpose of this survey is to present certain observations and facts, and not to enter this field of speculation. The observation that the groups of patients treated were skin sensitive to the colon bacillus does not imply necessarily that the therapeutic results obtained with *B. coli* vaccine were produced by an allergic mechanism. Until more is known about the fundamental nature of allergy and the differentiation between the allergic mechanism and non-specific protein reactions, any discussion bearing upon this point would be controversial.

#### METHOD OF VACCINE PREPARATION

Colon bacillus vaccine has been prepared according to the following method. The *B. Coli communis* and *communior* strains are mixed in equal proportion. A viable, rather than heat killed culture is detoxified, by subjecting it for fifteen hours to a one per cent concentration of purified and tested sodium ricinoleate, according to the recommendation of Larson (2) and of Dorst and Morris (3). The organisms then are washed several times with normal saline, to eliminate the sodium ricinoleate and its irritating effect. Finally, trikresol (0.4%) is added to

sterilize and preserve the vaccine. Vaccines containing the following total number of organisms per c.c. are prepared, viz: One, five, fifty, and five hundred thousand, five, fifty, and two hundred and fifty million, and one billion organisms per c.c. For the preliminary skin tests, separate preparations of a one billion concentration or less, of vaccine, (not detoxified), of each of the three stool organisms referred to above, have been used.

#### VACCINE DOSAGE, INTERVAL BETWEEN INJECTIONS AND METHOD OF ADMINISTRATION

If there has been no systemic reaction to the preliminary skin tests, the first subsequent vaccine injection consists either of 2 minims of a 50 million, or one minim of a 250 million concentration. In the occasional cases exhibiting a *marked*, temporary, systemic reaction to the skin tests, the first subsequent injection consists of two minims of one of the more dilute preparations, e.g., the five or fifty thousand dilutions. If a systemic reaction occurred, but was only slight to moderate in degree, the first dose following the skin tests is intermediate between those mentioned above.

Each subsequent increase of dose will vary with the patient's response to the last previous injection. Valuable information regarding the tolerance for vaccine of each individual patient has been obtained, by maintaining a special form with a detailed record of any temporary reaction to each vaccine injection and of any improvement of symptoms following it. The dose is increased *gradually*, during the first three or four injections particularly. It is desirable that each dose should be a little under, rather than over, the patient's full tolerance at the time. On the other hand, it has become apparent that the best results are obtained if the dosage is not too far below the patient's full tolerance. The matter of determining the optimum dose each time is of cardinal importance; the following, further, empirical observations are of great help in making this decision.

If, for 12 to 24 hours following the last injection, the patient has had no systemic reaction, or else only transient fatigue, the dose has not been increased too rapidly. On the other hand, if the reaction to any injection consists of marked malaise, lasting 3 or 4 days, this dose was too large. In this case the next dose should be reduced, and a further interval of several days should be allowed before giving it. If there has been any appreciable reaction to any injection, further vaccine should never be given until the patient has completely recovered and has had one or two good days. In several very unusual cases of "unstable" colon, such an infinitesimal dose as one minim of a dilution containing only 1,000 organisms per c.c. repeatedly and consistently produced transient colon pain. Furthermore, it should be noted that if a large dose of *B. coli* vaccine is administered to a particularly hypersensitive individual, transient fever may result, with subsequent aggravation of unstable colon and related symptoms, persisting occasionally for one or two weeks. *B. coli* vaccine should be *discontinued* in those occasional cases, for whom it is impossible, even by marked reduction of dosage, to avoid disagreeable and prolonged reactions.

As noted above, it is essential in this particular type of vaccine-therapy to individualize the dose to each patient's tolerance, rather than trying to follow a set schedule. However, it is important to know the in-

crease of dose tolerated by the average patient. The following rate of increasing the dose is well tolerated by most individuals; *viz.*: 2 minims of a fifty million concentration for the first dose; 1½ minims of a two hundred and fifty million preparation for the second dose, and one minim of a one billion concentration for the third injection. Providing the above increase has been tolerated, the average case should receive, for the subsequent five to seven doses, an increase at each injection of 1 to 1½ minims of the one billion concentration. In such an average case, the ultimate or final dose would vary from 6 to 12 minims of the one billion concentration. Many cases need a more gradual increase of dose. In other types of vaccine, to which the patient has little or no skin sensitivity, a dose of the above final amount, *viz.*, 6 to 12 minims, is sometimes given as an initial dose. Most undesirable and prolonged reactions would occur frequently if such initial doses of *B. coli* vaccine were administered.

Cases of chronic functional diarrhea usually tolerate at least average doses of *B. coli* vaccine; whereas cases of toxic vertigo and chronic headaches should receive, at the onset of treatment, doses below the average, to avoid temporary aggravation of symptoms. In cases of "unstable" colon the well tolerated initial dose varies considerably.

In most instances the therapeutic results of *B. coli* vaccine are more striking and persist longer in those cases that either have or develop an average tolerance for the vaccine, than in those tolerating only minute doses. However, there are exceptions to this rule.

The common interval between vaccine injections has been four days. If very small doses are being given and are well tolerated, the interval should be reduced to two or three days. If large doses are being given, or if the last vaccine injection caused any appreciable reaction, the interval should be lengthened to five, six, or seven days or longer. In those cases receiving vaccine every four days, who note marked improvement for a couple of days and then a tendency to return of symptoms a day or two before the next injection, the interval between injections should be shortened.

Ordinarily all the vaccine injections, after the skin tests, have been given *intramuscularly*. However, more recently, the several initial injections, involving only a small volume of 1 to 2 minims, have been given *intracutaneously*, and all subsequent larger volumes *intramuscularly*. The purpose of this modification is to increase the effectiveness of the vaccine and to avoid reactions.

Before instituting vaccine therapy in any case the individual should be informed that a slight temporary reaction may occur after any one of the several initial injections, while the dose tolerated is being determined. *B. coli* vaccine should not be administered unless one is conversant with the above facts regarding dosage.

#### TYPE OF CLINICAL MATERIAL UTILIZED

Any attempt to evaluate the effects of a new therapeutic agent upon the symptoms of an underlying functional condition is difficult, and fraught with possible pitfalls in interpretation. The danger of underestimating psychological influence is recognized fully. In order to put *B. coli* vaccine to a severe test, and to eliminate any favorable results not related to this

type of therapy, 125 long-standing, *chronic* cases of headache, functional diarrhea, "toxic vertigo," and "unstable" colon have been selected for vaccine therapy. Obstinate cases of this type do not represent enthusiastic individuals susceptible to mental suggestion. Definite and prompt improvement or disappearance of symptoms, in such groups of cases, following the introduction of a single therapeutic agent, usually is significant. Only these 125 cases, divided into the above subgroups, are analyzed in the tables presented.

In the groups of chronic headache and unstable colon cases, the conditions under which *B. coli* vaccine was administered were rigidly controlled by the fact that these cases had *previously received* comprehensive therapy in this Clinic, and had resisted it with definite *persistence of symptoms*. The fact that vaccine therapy was introduced subsequently as the only new therapeutic measure allows critical deductions to be drawn from the identification of vaccine results.

In the groups of long-standing, chronic diarrhea and chronic "toxic vertigo" cases, the direct effects of vaccine therapy have been controlled in a different manner, *viz.*, by starting the *B. coli* vaccine *in advance* of any other therapeutic measures and noting the effect of the vaccine alone.

During the past four years a *total* of over 1000 cases has been treated with colon bacillus vaccine. Since the indications for, and value of, *B. coli* vaccine therapy have become apparent from a critical study of the above subgroups of cases, vaccine has been started frequently at the onset of therapy, along with other measures, in those cases who probably would need vaccine sooner or later, or, at least, benefit from it. In the larger subgroup of over 800 cases, it no longer appeared advisable, in the best interest of the patients, to continue separating rigidly vaccine therapy from other indicated treatment, merely to provide an unnecessarily large group of cases from which to draw convincing deductions. In this latter group, an effort was made, rather, to expedite as much as possible the maximum improvement of symptoms. In many cases within this large group, it was interesting to note the repeated spurts of improvement occurring after each subsequent vaccine injection when no additions were being made to the remaining treatment.

#### RESULTS OF *B. COLI* VACCINE THERAPY

(a) *Chronic functional diarrhea group.* As to the specific indications for colon bacillus vaccine therapy, the group of chronic functional diarrhea cases should be mentioned first. The therapeutic results are quite striking and constant in this group; and in the marked cases, *B. coli* vaccine constitutes a very valuable therapeutic agent.

The first case treated with *B. coli* vaccine was an isolated case, a middle-aged woman who was admitted to the hospital in an emaciated and dehydrated state *nine* years ago. Clinical examination, repeated warm stool and proctoscopic examinations, stool cultures, and barium enema failed to show any evidence of an organic basis for the frequent and profuse diarrhea. This symptom had been present for a number of years, but had been much more marked for several months. During a four week period almost every known therapeutic measure to relieve the diarrhea was utilized, finally including opiates. The patient's condition, however, steadily grew worse, and became critical. It was decided to try the effect of an autogenous stool vaccine, the colon bacillus being the only organism recovered in this instance. To the surprise of

everyone, the diarrhea promptly stopped; and, in a short period, the patient was restored to excellent health. At the time, it was felt that this was probably an unique case with an unusual etiology.

During the past four years, however, a group of thirty cases with chronic functional diarrhea has been treated with colon bacillus vaccine. Although none of the subsequent cases has been so acutely ill as the one referred to above, similar striking therapeutic results have been obtained in the majority of cases.

This group of thirty cases has included 13 males and 17 females. The average duration of the diarrhea was 3½ years, one patient having had the symptom for 20 years. There was an average number of 5.3 stools per day, per patient. The proctoscopic findings were essentially normal in 86% of the cases; there was only slight injection of the rectal mucosa in the remainder. With the exception of increased mucus in 60%, the stool findings were otherwise normal throughout. Barium enema examinations revealed evidence of hypertonus of the colon in 83% of the group. A positive skin reaction to *B. coli* vaccine was obtained in 100% of the cases. Skin sensitivity to the other common stool bacteria was much less frequent and less marked. (See Table II).

TABLE II

*Skin Sensitivity to Stool Stool Vaccines in 30 Cases of Chronic Functional Diarrhea*

| Vaccine Used                 | Cases with + Skin Reaction | Moderate to Marked + Skin Reaction |
|------------------------------|----------------------------|------------------------------------|
| <i>B. Coli</i>               | 100%                       | 89%                                |
| <i>Staphylococcus Aureus</i> | 48%                        | 29%                                |
| <i>Streptococcus Fecalis</i> | 44%                        | 18%                                |

Colon bacillus vaccine therapy was started in advance of any other therapeutic measures in 29 of the 30 cases. In the other single case, the order was reversed, and comprehensive treatment was instituted first, with no improvement. Vaccine skin tests were then carried out in this case, and the diarrhea stopped promptly after this single dose of *B. coli* vaccine.

The degree of improvement of the diarrhea following vaccine therapy in this group of 30 cases is summarized in Table III. The time of onset of demon-

TABLE III

*Chronic Functional Diarrhea Group (Results of *B. coli* Vaccine Therapy Upon 30 Cases)\**

| Degree of Relief | Number of Cases | Percentage of Total Cases |
|------------------|-----------------|---------------------------|
| ++++ (Complete)  | 18              | 60%                       |
| +++              | 6               | 20%                       |
| ++               | 3               | 10%                       |
| +                | 1               | 3½%                       |
| Total Improved   | 28              | 93½%                      |
| Unimproved       | 2               | 6½%                       |

\*Average duration of diarrhea prior to treatment was 3½ years. Average No. of stools was 5.3 per day.

strable improvement is noted in Table IV. In view of this experience it is obvious that colon bacillus vaccine possesses a unique value in the treatment of this condition.

In 2 of the total group of 30 cases, there was marked improvement of the diarrhea, occurring promptly after the first dose of *B. coli* vaccine contained in the

skin tests; and in two other cases, the diarrhea stopped completely and promptly after the skin tests had been carried out. In other words, 13 1/3% of the group, (4 cases), responded in this striking manner

TABLE IV

*Chronic Functional Diarrhea Group (Time of Onset of Improvement—30 Cases)*

| Onset of Definite Improvement           | No. of Cases | Percentage of Cases |
|-----------------------------------------|--------------|---------------------|
| After 1st injection (Skin tests)        | 4            | 13½%                |
| After 2nd injection                     | 8            | 26⅔%                |
| After 4th injection                     | 4            | 13½%                |
| After 5th, or some Subsequent injection | 12           | 40%                 |
| No Improvement                          | 2            | 6⅔%                 |

to the first injection of colon bacillus vaccine. Only two cases failed to show improvement. These were two individuals with unusually marked and uncontrolled nervous tension factors. One of them had an agitated mental depression. The diarrhea in the other case disappeared only when the patient was subsequently placed in bed and given sedatives. It recurred when the patient became ambulatory. These two cases illustrate the important rôle played by nervous tension in aggravating the diarrhea in certain instances.

Gastric achlorhydria was found in a small percentage of these diarrhea cases. Inasmuch as an effort was being made to test the effectiveness of the vaccine, dilute hydrochloric acid was not given to any of the cases with achlorhydria, excepting, unintentionally, to one case. The diarrhea cases were all treated with *B. coli* vaccine, regardless of whether achlorhydria was present or not. Those cases with achlorhydria responded to the vaccine in a manner similar to the other cases. There is no intention, however, to belittle or deny the well known therapeutic value of administering hydrochloric acid to cases of functional diarrhea presenting achlorhydria.

(b) "Toxic vertigo" group. Sixteen cases of chronic "toxic vertigo" were selected for evaluation of colon bacillus vaccine therapy. There were 9 males and 7 females. The average age was 46 years. The average total duration of the vertigo was 21 months. In 75% of these cases the vertigo was either marked or extreme. Constipation and colon distress were both present in 75% of the group. Any possible organic basis for vertigo was carefully ruled out. In this group *B. coli* vaccine therapy was instituted in advance of any other treatment. The therapeutic results are tabulated in Tables V and VI. The two cases

TABLE V

*Chronic "Toxic Vertigo" Group (Results of *B. coli* Vaccine Therapy—16 Cases)\**

| Degree of Relief | Number of Cases | Percentage of Total Cases |
|------------------|-----------------|---------------------------|
| ++++ (Complete)  | 9               | 56%                       |
| +++              | 3               | 19%                       |
| ++               | 2               | 12%                       |
| Total relieved   | 14              | 87½%                      |
| No Relief        | 2               | 12½%                      |

\*Average duration of vertigo prior to therapy was 21 mos.

obtaining no relief were very nervous individuals. Furthermore, nervous tension was present in certain of the cases obtaining partial, but not complete, relief.

(c) *Chronic headache group.* Twelve cases presenting chronic headache as the main complaint, who had obtained no relief from a comprehensive course of therapy, subsequently received *B. coli* vaccine therapy. The average total duration of headache in these cases was 11.7 years. The average age was 41 years. The location of the headache was variable. In 83% of the

TABLE VI

*Chronic "Toxic Vertigo" Group (Time of Relief With B. coli Vaccine—16 Cases)*

|                                   |                 |
|-----------------------------------|-----------------|
| A. Time of Onset of Relief        |                 |
| (1) After 1st vaccine injection — | 12½% of cases   |
| (2) After 3rd vaccine injection — | Most frequently |
| B. Time of Maximum Relief         |                 |
| (1) After 9th vaccine injection — | Most frequently |

cases the headache was severe. There was associated constipation in 92%, and colon distress in 66% of this group. Some of these patients had noted aggravation of headaches when constipated; but frequently the headaches were present during periods of apparently normal bowel function. Only 2 of these cases had classical migraine features. Any possible organic basis for headaches was ruled out in each instance.

The unsuccessful program of general treatment preceding vaccine therapy in this group was directed particularly toward the correction of constipation and the reduction of nervous tension. *B. coli* vaccine therapy was introduced subsequently as the only new therapeutic measure.

Nine of the twelve cases (75%) obtained prompt, complete, and most gratifying relief from vaccine therapy. (See Table VII). One woman in this group,

TABLE VII

*Chronic Headache Group \* ÷ (Results of B. coli Vaccine Therapy—12 Cases)*

| Degree of Relief | Number of Cases | Percentage of Total Cases |
|------------------|-----------------|---------------------------|
| ++++ (Complete)  | 9               | 75%                       |
| No Relief        | 3               | 25%                       |

\*Average duration of headache prior to vaccine treatment was 11.7 years.

†An additional group of 27 cases of chronic headache also received *B. coli* vaccine.

who had had almost constant headache for 20 years, reported 13 months later that she had enjoyed complete freedom of headache for this entire period following vaccine treatment. Three cases obtained no apparent relief. In two of these three cases there was obvious uncontrolled nervous tension.

In a group of 27 additional cases of chronic headaches, similar relief followed vaccine therapy in a high percentage of the cases. However, these cases cannot be included in the above group, since vaccine therapy in this group was not sharply separated from other treatment. However, convincing spurts of improvement occurred after successive vaccine injections, when no additions were being made to the remaining therapy.

(d) *Combined "toxic vertigo" and chronic headache group.* A group of 8 cases was studied, who had suffered for an average of 4 years from a combination of headache and "toxic vertigo." This group received

colon bacillus vaccine in advance of any other therapeutic measures. Definite deductions can, therefore, be drawn. In seven of these eight cases, either marked or complete relief was obtained following vaccine therapy. (See Table VIII).

TABLE VIII

*Combined "Toxic Vertigo" and Chronic Headache Group\* (Results of B. coli Vaccine Therapy—8 Cases)*

| Degree of Relief From Both Symptoms | Number of Cases | Percentage of Total Cases |
|-------------------------------------|-----------------|---------------------------|
| Either Marked or Complete Relief    | 7               | 87½%                      |
| No Relief                           | 1               | 12½%                      |

\*Average duration of symptoms prior to treatment was 4 years.

(e) *Obstinate spastic constipation group.* In the occasional cases of obstinate spastic constipation, in which normal bowel function was not obtained from the usually successful physiological therapy, colon bacillus vaccine has been administered subsequently. In most of these cases, excellent results have been obtained in breaking into the vicious circle and relieving the constipation. A number of patients have testified spontaneously, after a few vaccine injections, that the calibre of the stools had changed suddenly from small calibre to a normal diameter. In some cases, a "repeat" barium enema has been obtained after vaccine therapy, and has shown a disappearance of the marked narrowing of the distal colon, noted in the earlier film. These two sources of evidence both indicate that colon bacillus vaccine tends to reduce colonic spasm.

It is not surprising that the same type of vaccine therapy tends to relieve both chronic functional diarrhea and chronic spastic constipation; for in both instances, there is hypertonus or spasm of the intestinal musculature. In this connection, it is a well known fact that diarrhea and spastic constipation not infrequently alternate in the same individual.

(f) *Chronic "unstable colon" (non-ulcerative colitis) group.* In view of the gratifying results tabulated above in the treatment of simple alternations of colon function, such as chronic diarrhea and obstinate spastic constipation, it is not surprising that therapeutic aid has been obtained also in cases presenting a combination of altered bowel function and colon distress or pain.

In the majority of cases of unstable colon, the distress or pain, and associated symptoms, will clear up satisfactorily with a well planned comprehensive program of therapy. On the other hand, in a subgroup of cases with unusually marked symptoms, general treatment fails, in certain instances, to produce satisfactory results.

In order to subject colon bacillus vaccine therapy to a severe test in the treatment of the unstable colon, 59 obstinate cases, whose symptoms had not disappeared following comprehensive therapy, subsequently were given a course of *B. coli* vaccine. These 59 obstinate cases were selected from a very large group of cases, the majority of which had responded satisfactorily to comprehensive therapy.

The comprehensive program had consisted of physiological regulation of the bowels, a bland but well balanced diet with adequate vitamin content, elimination or reduction of neurogenic factors, so far as



possible, correction of faulty habits, antispasmodics, and, in some instances, changing the stool flora with lactodextrin and acidophilous milk. Recently sodium ricinoleate has been added, as noted below, to this comprehensive regime.

The presence or absence of improvement in the 59 obstinate cases, and the degree of partial improvement, following the comprehensive treatment, (without vaccine), are summarized in Table IX. When vaccine

TABLE IX

*Unstable Colon Group (Non-Ulcerative Colitis) (Results of Comprehensive Therapy—59 Obstinate Cases)\* (No Vaccine Therapy Administered)*

| Degree of Relief of Colon Distress, etc. | Number of Cases | Percentage of Total Cases |
|------------------------------------------|-----------------|---------------------------|
| 0                                        | 22              | 37%                       |
| +                                        | 7               | 12%                       |
| ++                                       | 23              | 39%                       |
| +++                                      | 7               | 12%                       |
| ++++                                     | 0               | 0                         |

\*This group of obstinate cases constitutes the clinical material for subsequent *B. coli* vaccine therapy.

therapy was administered subsequently, as the only new therapeutic agent, the resulting presence or absence, and the degree, of further improvement in the same group of cases are reviewed in Table X. It is

TABLE X

*Unstable Colon Group (Non-Ulcerative Colitis) (Results of Subsequent B. coli Vaccine Therapy Upon Colon Distress Persisting After Comprehensive Treatment—59 Cases Referred to in Table IX)*

| Degree of Relief                           | Number of Cases | Percentage of Total Cases |
|--------------------------------------------|-----------------|---------------------------|
| From 0 to +                                | 2               | 4%                        |
| From 0 to ++                               | 5               | 8%                        |
| From 0 to +++                              | 6               | 10%                       |
| From 0 to ++++                             | 6               | 10%                       |
| From + to ++                               | 1               | 2%                        |
| From + to +++                              | 5               | 8%                        |
| From + to ++++                             | 1               | 2%                        |
| From ++ to +++                             | 6               | 10%                       |
| From ++ to ++++                            | 8               | 14%                       |
| From +++ to ++++                           | 1               | 2%                        |
| Total Cases Improved                       | 41              | 70%                       |
| Symptoms Unchanged                         | 13              | 22%                       |
| Symptoms Aggravated Temporarily by Vaccine | 5               | 8%                        |

significant that 31 of the 41 cases showing improvement after vaccine therapy, showed a moderate to marked degree of improvement over that previously resulting from comprehensive treatment in the same group of cases.

#### SODIUM RICINOLEATE IN IRRITABLE COLON THERAPY

In the small group of "unstable" colon patients who presented *extreme* hypersensitiveness to *B. coli* vaccine, withholding vaccine and giving sodium ricinoleate by the mouth is, in our experience, the most effective therapeutic measure found thus far. Furthermore, the earlier observations of Morris and Dorst (3) have been confirmed, namely, that sodium ricinoleate is of real value in the routine, early treatment of "unstable" colon cases. These Authors maintained that better results can be obtained, if this preparation is added to the therapeutic program to supplement the effect of the stool vaccine. During the past year at

least one five grain capsule of sodium ricinoleate routinely has been given in these cases just before breakfast each morning, and in a number of instances, a second capsule before dinner, as an important initial addition to the program of comprehensive treatment. Sodium ricinoleate therapy has been continued usually for several months. It is especially helpful in relieving colon pain or distress. In fact, since sodium ricinoleate has been added to the routine comprehensive program, *B. coli* vaccine has been needed somewhat less frequently for the relief of colon pain. Recently sodium ricinoleate therapy also has been added routinely to the vaccine treatment of the functional diarrhea, toxic vertigo and chronic headache groups, to further increase the effectiveness.

It has been shown definitely that sodium ricinoleate has a detoxifying effect upon the bacterial protein or toxins (2) and vaccines (3). Doubtless, an essentially similar effect is produced upon the mass of bacterial protein in the intestinal tract. However, the exact mechanism by which sodium ricinoleate produces its desirable therapeutic effect is not definitely known.

(g) *Pylorospasm group*. The localized epigastric distress, which frequently accompanies "unstable" colon distress, tends to respond to *B. coli* vaccine in a manner similar to that of colon distress. Furthermore, certain instances of functional epigastric distress, unassociated with colon distress, and persisting after comprehensive treatment, have then received *B. coli* vaccine therapy, with resulting disappearance of this distress.

#### GENERAL EFFECTS OF COLON BACILLUS VACCINE THERAPY

Aside from the effects noted above, *B. coli* vaccine therapy has been noted to have certain important and gratifying side effects. These occur much too frequently, when vaccine therapy is employed, to be explained a mere coincidence. Many of these patients report a striking improvement in their general feeling of well being, such as they have not noted in many years. This subjective relief often is reflected in their general appearance, increased appetite and, in some cases, in increase in weight.

#### INDICATIONS FOR COLON BACILLUS VACCINE THERAPY

(1) All cases of chronic functional diarrhea should receive *B. coli* vaccine, unless one encounters a rare case presenting some contra-indication.

(2) All cases with either chronic "toxic vertigo," or the type of chronic headache which tends to be associated with colon distress or constipation, should receive *B. coli* vaccine, unless contra-indicated.

(3) In the unusual cases of obstinate spastic constipation, not yielding satisfactorily to other measures, *B. coli* vaccine is helpful in breaking into the vicious circle.

(4) In the obstinate cases of "unstable" colon, (non-ulcerative colitis), not responding satisfactorily to the commonly employed comprehensive treatment, definite help will be obtained from *B. coli* vaccine in the majority of cases, provided the vaccine is tolerated.

(5) Providing no contra-indication exists, most cases of unstable colon presenting marked colon pain or distress, will show more prompt and pronounced improvement if a course of vaccine therapy is in-



stituted at the onset of treatment, along with the comprehensive program. However, one can wait, if desired, to select only the obstinate cases for vaccine.

It is not necessary to administer *B. coli* vaccine in any routine manner to cases of "unstable" colon, since the majority of these cases clear up satisfactorily with comprehensive therapy alone.

#### LIMITATIONS OF COLON BACILLUS VACCINE THERAPY

1. The most important limitation rests in the observation that the desirable therapeutic effects obtained are not permanent. If one gives a single course of vaccine therapy, with no follow-up injections, after four to twelve months numerous patients note the good effect of the vaccine "wearing off." However, in those patients whose original symptoms were distressing and persisted after other therapeutic measures, and whose subsequent relief with vaccine was marked, frequently advice has been given to *avoid* subsequent loss of the vaccine effect, by obtaining a single vaccine injection about once a month. Patients obtaining such relief, and later having a recurrence of symptoms, frequently have *requested* further periodic vaccine injections. In such instances the dose can and should be maintained at a level sufficiently high to retain the benefit gained. As a rule, this subsequent optimum monthly dose is between 50 and 100% of the last maximum tolerated dose of the *course* of injections.

On the other hand, in many cases the vaccine seems to break a vicious circle, which is not re-established. In this latter group, if the patient adheres to the comprehensive treatment, the subsequent course continues satisfactory over an indefinite period without further vaccine.

2. The fact that *B. coli* vaccine is contra-indicated definitely in certain cases constitutes the second limitation. (See below).

3. In the unstable colon group the relief of pain or distress following vaccine does not occur in quite as high a percentage of cases as the relief of symptoms in the other groups of cases referred to above. In the unstable colon group, it is not always possible to prognosticate, in the individual case, the *exact degree* of improvement to be expected from vaccine. Vaccine produces brilliant results in some cases; whereas, in other cases, there is moderate or else no apparent improvement. This fact would suggest some variation, in different patients, in the *relative* importance of the particular etiological factor, which is favorably affected by *B. coli* vaccine.

#### CONTRA-INDICATIONS FOR COLON BACILLUS VACCINE THERAPY

1. In those cases of unstable colon presenting an associated chronic infectious arthritis, *B. coli* vaccine, in ordinary dosage, is definitely contra-indicated. Even though there be no active arthritis at the time, if there is a definite history of infectious arthritis, it is advisable, as a rule, to omit vaccine. In this particular group of cases, a single injection of *B. coli* vaccine very occasionally has induced a temporary flare-up of a quiescent arthritis.

In cases with no evidence of an arthritic tendency, on rare occasions, following a *B. coli* vaccine injection, slight *transient* joint pain, lasting a day or two, has been encountered. In such cases vaccine therapy has been discontinued at this point.

2. In the *occasional* cases of unstable colon, not tolerating even *minute* doses of *B. coli* vaccine, and having a disagreeable general reaction, with temporary aggravation of distress or pain, this type of therapy should be *discontinued* promptly. (If doses of *average* size are not tolerated at the onset, the dose should be decreased to a very small amount, and subsequent doses should be increased *gradually*, to avoid further reaction).

3. In the rare cases presenting a history of a marked tendency to urticaria, any *average* dose of colon bacillus vaccine should be considered with *caution*. A flareup of this condition may result from *B. coli* vaccine. (On the other hand, *minute* doses of this vaccine have been of marked therapeutic value in certain cases of urticaria).

4. If a head cold exists, or any other acute infection, no *B. coli* vaccine should be given until the acute infection has subsided.

#### SUMMARY

(1) The observations and conclusions outlined amplify and supplement those presented by the same Authors in an earlier publication. In this previous survey, the Authors' experience with autogenous polyvalent stool vaccine therapy was reviewed. These vaccines contained those organisms to which the patient was skin-sensitive.

(2) For several reasons it was suspected that similar favorable vaccine results might be obtained by administering *B. coli* vaccine alone. (This organism had been included in almost 100% of the polyvalent vaccines previously used). By instituting the use of stock *B. coli* vaccine, about four years ago, this method of vaccine therapy was simplified and rendered more practical. No resulting demonstrable loss of therapeutic effectiveness has been noted.

(3) Of three thousand cases, presenting one or more of the related chronic functional disorders referred to in this survey, 99% have yielded a positive skin reaction to *B. coli* vaccine. As a rule, the skin reaction has been marked. There is no desire, however, to enter the field of speculation, as to whether or not the desirable therapeutic results obtained have been produced through the operation of an *allergic mechanism*. The purpose of this survey simply is to present certain observations and facts relating to the therapeutic results obtained from *B. coli* vaccine.

(4) The colon bacillus vaccine has included both strains of the organism. The viable culture has been detoxified by exposure to sodium ricinoleate; and the organisms have been killed then with 0.4% trikresol.

(5) In administering *B. coli* vaccine, it is essential to individualize the dose for each patient, if satisfactory results are to be obtained. Overdosage tends to cause temporary aggravation of symptoms. Detailed information is outlined above, as to the method of determining or approximating the optimum dose for successive injections in each case. *B. coli* vaccine should not be used unless one is conversant with these facts regarding dosage.

(6) A total of more than 1,000 selected cases have been treated with *B. coli* vaccine during the past four years. These cases have included chronic functional diarrheas, cases with chronic "toxic vertigo," instances of long standing headaches of the type usually associated with chronic constipation or colon distress, and

selected cases of marked or obstinate "unstable" colon. (Chronic non-ulcerative colitis).

In 125 of these chronic and obstinate cases the conditions under which vaccine therapy was administered were rigidly controlled, so that critical deductions may be drawn as to the validity of vaccine results. In certain subgroups, vaccine treatment has been instituted *in advance* of other treatment. In the other subgroups, vaccine therapy has been *postponed*, and subsequently instituted in those obstinate cases whose symptoms have *persisted* after receiving comprehensive therapy. In either instance one can *identify* the results directly traceable to *B. coli* vaccine therapy.

In the larger group of over 800 cases treated subsequently with vaccine, vaccine therapy has been instituted at the onset, along with other therapeutic measures, for reasons specified. Although these cases cannot be included, for obvious reasons, in the groups of cases critically analyzed, it was interesting to note in this large group the repeated spurts of improvement occurring after successive vaccine injections, when no additions to the remaining treatment were being made.

(7) Thirty cases of chronic functional diarrhea, with an average duration of  $3\frac{1}{2}$  years, received *B. coli* vaccine in advance of any other therapy. There was improvement of the diarrhea in a total of 93  $1\frac{1}{3}\%$  of this group. There was complete disappearance of the diarrhea in 60%, and a marked degree of improvement in another 20% of the group. In 40% of the cases demonstrable improvement was noted after either the *first* or *second* vaccine injection.

(8) In the chronic "toxic vertigo" group, a total of 87½% of the cases obtained relief from *B. coli* vaccine.

(9) In a group of cases with chronic headache, with average duration of 11.7 years, and of the type usually associated with chronic constipation or colon distress, 75% obtained *complete* relief from *B. coli* vaccine.

(10) In a group of cases presenting a *combination* of toxic vertigo and chronic headache, of 4 years duration, either marked or complete relief occurred in 87½% of the cases.

(11) In the occasional cases of *obstinate* spastic constipation, when *B. coli* vaccine is added to the comprehensive therapy previously instituted, there is convincing evidence that the vaccine tends to relax the partially obstructing spasm of the distal colon.

(12) In fifty-nine selected cases of "unstable" colon, (non-ulcerative colitis), with obstinate distress or pain, which persisted in spite of the usual comprehensive therapy, *B. coli* vaccine was instituted subsequently. In 70% of this group there was either improvement or disappearance of the colon distress.

(13) The specific indications for *B. coli* vaccine treatment are summarized and emphasized.

(14) The limitations of *B. coli* vaccine therapy, and the contra-indications to its use, are outlined and discussed.

(15) *B. coli* vaccine constitutes a valuable therapeutic aid, if *judiciously* used in properly selected cases. In cases with chronic functional diarrhea, chronic "toxic vertigo," and chronic headaches of the type designated, the therapeutic results of *B. coli* vaccine are striking. In selected, obstinate or marked cases of unstable colon, *B. coli* vaccine is usually of

definite value. (The *majority* of cases of unstable colon can be treated satisfactorily without vaccine, through the aid of the specified comprehensive program of treatment).

## REFERENCES

1. Mateer, J. G., and Baltz, J. L.: An Evaluation of Stool Vaccines in Chronic Irritable Colon Therapy. *Annals Int. Med.*, Vol. V, 982-991, 1932.
2. Larson, W. P., and Eder, H.: Immunization Against Diphtheria with Toxin Detoxified with Sodium Ricinoleate. *J. A. M. A.*, Vol. 86, 998-1000, 1926.
3. Dorst, S. E., and Morris, R. S.: Bacterial Hypersensitivity of the Intestinal Tract. *Am. Jour. Med. Sci.*, Vol. 180, 650-656, 1930.

## DISCUSSIONS:

DR. LEON SCHIFF (Cincinnati): During the past seven years or more, due chiefly to the work of Drs. Morris and Dorst, which is being continued by Dr. Dorst, a great many patients with unstable colon and its various manifestations have received injections of *autogenous* stool vaccine, containing organisms selected after preliminary skin testing. While the results have not been tabulated, they have been frequently striking; but no more so than those reported by Dr. Mateer and his associates from the use of *stock* vaccines. This confirms the Authors' own observations and tends to show that the benefits may be due to non-specific rather than specific allergic factors.

The experience in Cincinnati has been similar to that of Dr. Mateer and his associates, namely, that those individuals who are unable to receive the average dose of vaccine because of hypersensitivity, derive less benefit than those who can receive the average or larger doses. Recently, Dr. Dorst has been using urea and nascent nitrous acid in place of sodium ricinoleate as a detoxifying agent, and feels that by this means greater detoxification may be accomplished, thus enabling the patient to tolerate larger doses. The fact that urea acts as a detoxifying agent may be of interest in connection with some of the remarks our President made this morning regarding the detoxifying function of the liver.

The prompt disappearance of diarrhea associated with achlorhydria, following the use of vaccine is extremely interesting.

Dr. Mateer and his associates consider the existence of arthritis as a contraindication to the use of colon bacillus vaccine. Drs. Freiberg and Dorst are using autogenous stool vaccines in a large series of arthritic cases, mostly of the infectious form. They have found it necessary to use smaller doses because of the risk of inducing a flare-up of symptoms. Accordingly, suboptimal doses are given over a longer period of time, extending frequently over many months.

The Authors mention the oral use of sodium ricinoleate ("Soricin"), in five grain doses, to relieve the pain of unstable colon. We are using ten grain doses three times a day. It is necessary to give the Soricin in an enteric-coated medium, as it is said to be inactivated by the hydrochloric acid of gastric juice. Berger has reported a decrease in sensitivity to stool organisms, following the prolonged use of Soricin, as determined by repeated intradermal tests.

Dr. Mateer and his associates have presented a painstaking study, carried out over a period of years, with very encouraging results. Having twice visited their Clinic, and being aware of the care with which their observations are made, I feel that they are to be complimented and that their work should receive serious consideration and wider clinical application.

DR. SARA M. JORDAN (Boston): I feel very inadequate in the rôle of discussant of this very carefully prepared paper of Dr. Mateer's, because I am not familiar with this form of therapy in this condition. I can't either confirm or disagree with Dr. Mateer's findings here, but when the term "unstable colon" is mentioned, I do like to say a few words about it.

By the way, we are indebted to Dr. Kantor for that term "unstable colon." We called it the irritable colon, but he suggested because it isn't always hyper-irritable, it should not be called irritable but unstable. I think, to Dr. Mateer and to all of us who have used the term, it means a disturbance in the tonus and in the irritability of the colon, and probably of the whole digestive tract, but in the colon it is more easily visualized than in the small intestine and in the stomach.

It is an important condition, of course, because I think perhaps all of you have had the experience of finding that in the cases who come to you with gastro-intestinal disturbances, about 35 per cent have no organic disease, and they are not just neurotics; that is, we all find, that by directing attention and focussing our therapy on the digestive tract, and perhaps particularly on the colon, we are able to relieve not only the digestive symptoms, but also the associated neurogenic symptoms in a large number of cases.

Dr. Mateer has already said that the ordinary cases of irritable colon do not need anything more than what he calls the "comprehensive" treatment, and we also find that to be true. I will show you a slide which will show that there is a large group of cases, about 61 per cent in our group, who have no other symptoms except the digestive complaints. In about 39 per cent there are associated neurogenic symptoms. The relief of the abdominal symptoms and of the neurogenic symptoms is very often synchronous and well coordinated.

The use of colon bacillus therapy, it seems to me, has been shown by Dr. Mateer to be apparently very valuable in this group of cases which apparently is not amenable to the so-called comprehensive treatment.

DR. JOHN G. MATEER (closing the discussion): As to the use of colon bacillus vaccine in arthritis, until the last two years, we also have given this type of vaccine to

cases of "unstable" colon with an associated arthritis. There have been certain instances in which both the arthritis and colon condition were relieved in a striking manner following small doses of the vaccine. However, it was very difficult, from the standpoint of the arthritis, to estimate consistently the ideal dose, and to select a sufficiently small dose to avoid a certain number of disagreeable flareup of a quiescent arthritis. In view of this experience, we now regard the presence of an associated arthritis as an important contra-indication to the use of *B. coli* vaccine. This viewpoint seems valid, inasmuch as recent advances in the treatment of arthritis along other lines, *e.g.*, in relation to diet, have rendered the treatment of chronic infectious arthritis reasonably satisfactory, without resorting to the risk of vaccine therapy.

In other words, we agree with the experience of Dr. Dorst, referred to by Dr. Schiff, that certain cases of associated arthritis may obtain striking improvement following minute doses of *B. coli* vaccine treatment. However, the risk of encountering overdosage before the course of injections is completed is appreciable; and, in such cases, the flareup of arthritic symptoms may persist for some time.

We also agree with Dr. Schiff in his remarks relative to the dosage of "Soricin," or sodium ricinoleate, as recommended by Dr. Dorst. There are some cases in which the small and probably ultra-conservative dose of one 5 grain capsule a day is insufficient to afford satisfactory relief of the unstable colon distress. In such cases we have increased the dose to two or three capsules a day, administering one capsule just before each meal.

In conclusion, we should like to state that colon bacillus vaccine therapy is not a panacea; but, if judiciously employed, it is an important additional therapeutic agent for a group of cases in which supplementary aid is needed.

## ABSTRACTS

CLUTE, HOWARD M., M.D., F.A.C.S., AND  
SWINTON, NEIL W., M.D.

*Exploration of the Common Duct in Gall Stone Surgery. S. G. and O., Vol. 59, No. 6, pp. 906-912, Dec., 1934.*

This article is a discussion of the indications for exploration and drainage of the common bile duct, a detailed description of the operative technique as used at the Lahey Clinic at the present time, and a report of the end results obtained between the years 1910 and 1934.

The common duct should be drained for the following indications: (1) The presence of jaundice, either in the history or at the time of examination. The point is emphasized that between thirty to forty per cent of patients having common duct stones have had no jaundice at any time. (2) The presence of a small thick-walled, contracted gall bladder. (3) The presence of thickening or stone along the gall bladder or in the head of the pancreas as evidenced by palpation of the duct, or dilatation of the common duct. (4) The presence of small stones in the gall bladder or in the cystic duct which

might easily pass into the common duct.

Spinal anesthesia is the anesthesia of choice in good risk patients where the operation is expected to last one hour or less. For the poor risk patients and where undue technical difficulties are anticipated, intratracheal ethylene anesthesia with regional field block is preferable.

The operative technique will not be reviewed in detail in this abstract. Adequate exposure of the common duct is first obtained, the cystic artery is ligated, following which a longitudinal incision is made in the common duct one to two centimeters above the ampulla and the duct is carefully explored through this incision. Following exploration and the removal of stones if present, a small T-tube is placed in the duct and closure made about this T-tube.

Following operation, after the first week, the tube is gradually clamped off and when the stools are colored and all bile is passing through the common duct into the intestine, the T-tube is removed.

At the present time, at the Lahey Clinic, common ducts are being explored in between thirty-five and forty per cent of the cases of gall stones. Common duct stones are being found in between eighteen to twenty-one per cent of those cases having the common duct explored.

The Authors report that from 1910 to 1934, at the Lahey Clinic, cholecystectomy has been done 1543 times. In this series, the common duct was drained 434 times. The mortality in all gall stone operations was 3.8 per cent. In the gall stone group where the common duct was drained, the mortality was 4.83 per cent, and in those cases in which the common duct was not opened, the mortality was 3.61 per cent. In those cases in which the common duct was explored but no common duct stones were found, the mortality was .25 per cent.

Stricture of the common duct has never resulted following exploration by this technique. It has not been felt that exploration of the common duct has increased operative mortality in this group of cases.

N. W. Swinton, Boston.

## SECTION VI—*Abdominal Surgery*

### Aseptic Electrosurgical Enterostomy<sup>\*</sup>

#### A New Method

(Preliminary Report)

By

LESTER R. WHITAKER, M.D.

BOSTON, MASSACHUSETTS

IT is generally agreed that whenever the bowel is unable to propel its content, enterostomy may be a life-saving procedure. This is particularly true in cases of obstruction of the small intestine where the patient is a poor risk, or in paralytic stasis from varied causes. Blockage of the colon by tumor, or otherwise, usually demands an enterostomy of some sort to obtain evacuation and return of normal tone preliminary to resection, as well as for prevention of post-operative distention with strain on the suture line.

Heretofore, an enterostomy has been a race between the surgeon and the bacteria to see whether the tube would go in before the content of the bowel came out. Usually the bacteria won, with more or less contamination of the operative site. Obviously an easily executed aseptic method of enterostomy is advantageous. An attempt at such a method will be described.

#### METHOD

The experimental apparatus consisted of a small rectal tube, cut off to a length of ten inches and the tip bevelled. Also a wire-loop electrode of the proper size with a handle of sufficient length to be put through the tube.

The trials were made upon the stomach of the dog: A stitch is taken in the wall of the stomach and tied; then the end of the tube is placed just proximal to it, and buried in the wall of the stomach by a continuous mattress or Lembert stitch for a distance of about one to one and one-half inches. The suture is held tightly around the tube to prevent leakage when the opening is made. The wire-loop tip of the electrode is bent a little to come into contact with the side of the tube. It is then inserted, and when by palpation it is felt to be in contact with the wall of the stomach at the end of the tube, the current is turned on from the

electrosurgical unit. The "cutting current" with low voltage and heavy dehydration is used. The object is to cut through the wall of the viscus, and at the same time to produce coagulation enough to stop bleeding from any vessels which might be encountered. For that reason the cutting must not be done too rapidly. More of a semi-cautery effect is desirable. The electrode is turned around to be sure to make a circular opening. Of course the anterior wall has to be held up in order to keep the electrode from damaging the opposite wall. With care, and avoiding too much pressure on the electrode, this is easily prevented. The free end of the tube is held out laterally over the edge of the wound to avoid contamination from escaping fluid. Then the electrode is withdrawn a little to bring it back just inside the tube. The handle acts as an obturator and gives the necessary stiffness for the tube to be pushed into the opening. This is done while the end of the suture is held taut to prevent leakage. Then the suture is tied in the tissues and the ends tied around the tube to hold it.

If the gut is distended it is preferable to insert a row of mattress sutures over the tube, and pull them up together—thus to distribute the tension and avoid tearing out of the sutures. If the tension is too great to allow suturing the wall of the gut over the tube the method described cannot be used.

The apparatus described is that used experimentally. The tube is perhaps a little too large for enterostomy in the small intestine of man. A smaller one could be used and an electrode with a thinner shaft made to fit into it. A tube even larger could be employed for a temporary colostomy or gastrostomy.

In gastrostomy, a comparatively avascular area for making the opening should be chosen. But, since the tube has to be inserted through an opening of smaller diameter in the stomach, there would be a tendency to occlude cut ends of vessels by pressure. For use on the small intestine and colon, however, there are no obvious dangers, and it appears that this aseptic method will be distinctly advantageous.

\*From the Evans Memorial of the Massachusetts Memorial Hospitals, Boston, Massachusetts.  
Submitted August 31, 1935.

## SECTION VII—*Surgery of the Lower Colon and Rectum*

### The Haemorrhoidal Lesion:

Its Radical Cure by Submucous Injections with or without the Ligature Operation.

By

E. A. DANIELS, M.Sc., M.D.  
MONTREAL, CANADA

A CONSIDERATION of the haemorrhoidal lesion, will readily demonstrate that operation will be adequate in effecting a cure in a large percentage of patients. However, recurrences will consistently present themselves in a group of cases, where the mucous membrane lesion is not recognized together with the haemorrhoidal varix. It is the recognition of this mucosal abnormality in relation to internal haemorrhoids, which forms the subject of the present study.

#### THE HAEMORRHOIDAL LESION

One is concerned with the gross haemorrhoidal lesion in this presentation; and in considering the gross pathology of internal haemorrhoids, one will recognize the soundness of the treatment presently to be described.

The *histological appearance* of internal haemorrhoids is sufficiently well known. The typical haemorrhoid consists of a mass of dilated venules, (arterioles are present but are few in number and are practically unchanged) distributed through a stroma of connective tissue which shows chronic inflammatory changes. The venous walls show thinning, the result of replacement of their muscular and elastic coats by fibrous tissue. The haemorrhoidal varix is covered by a diseased, thinned, granular, more or less redundant mucous membrane. Grossly, internal haemorrhoids must be regarded as dilatations of the internal (superior) haemorrhoidal plexus of veins which run quite superficially in the submucosa and which drain into the portal circulation. Because of their superficial distribution, very feeble support is offered to these veins and a dilated state in these vessels is easily arrived at. The mucosa of the lower rectum is very loosely attached by fibrous and elastic tissue to the submucosa. The superficial course of the tributaries of the superior haemorrhoidal vein in the lower rectum, very feebly supported by a loose, redundant, mucous membrane, renders these veins especially vulnerable to pathological changes. Gravity, and the fact that the portal vein and its larger tributaries are without valves, are other factors which favour a dilated venous state in the haemorrhoidal plexus. This dilatation is the initiation of the haemorrhoidal lesion with its various sequelae. This leads one to a gross consideration of the further evolution of the haemor-

rhoidal lesion and will furnish an explanation for the *rationale* of submucous injections of a sclerosing fluid with or without a subsequent ligature operation.

The haemorrhoidal lesion in its early stages may be observed as a dilatation of the radicles of the superior haemorrhoidal vein running in the columns of Morgagni of the lower rectum. The three larger tributaries of the superior haemorrhoidal vein are, a left lateral vessel, a right anterior and a right posterior one. These varices are covered by an unhealthy, redundant mucous membrane which has a hyperaemic, granular appearance. This type of case presents occasional rectal bleeding. This is the result of fecal trauma, which might occur from time to time when a hard fecal mass passes over the granular mucous membrane and produces a pin-point rupture of the mucosa and its underlying superficial vulnerable varix. The redundant mucosa soon overrides the tiny pin point rupture of the venous wall and arrests the bleeding. It is for this reason that the source of haemorrhoidal bleeding, can rarely be demonstrated during proctoscopic examination (1). When the haemorrhoidal lesion becomes well established, the mucous membrane redundancy becomes marked, and in some cases rises high up into the ampulla of the rectum, almost filling the lower rectum in concertina-like fashion. One is now dealing with an actual mucous membrane prolapse. This prolapse is usually not extruded because of the competency of the anal outlet. (The external sphincter, the internal sphincter, which is the lower thickened circular fibres of the bowel wall and the *levator ani*). In this type of case, upon proctoscopic examination of the lower rectum and anal canal, one will find the three primary internal haemorrhoids, a left lateral varix, a right anterior and a right posterior one, all three varices being covered by a granular hyperaemic mucous membrane. These haemorrhoids may or may not be extruded with bowel movements and may or may not require reduction, depending primarily upon the degree of muscle tone of the anal outlet. These three varices will be found running up the bowel from the pectinate line (*i.e.*, the base of the columns of Morgagni, at the ano-rectum), and at their lower borders may have become epithelialized because of continual extrusion. These haemorrhoids are covered by columnar epithelium since one is dealing with internal haemorrhoids of the lower

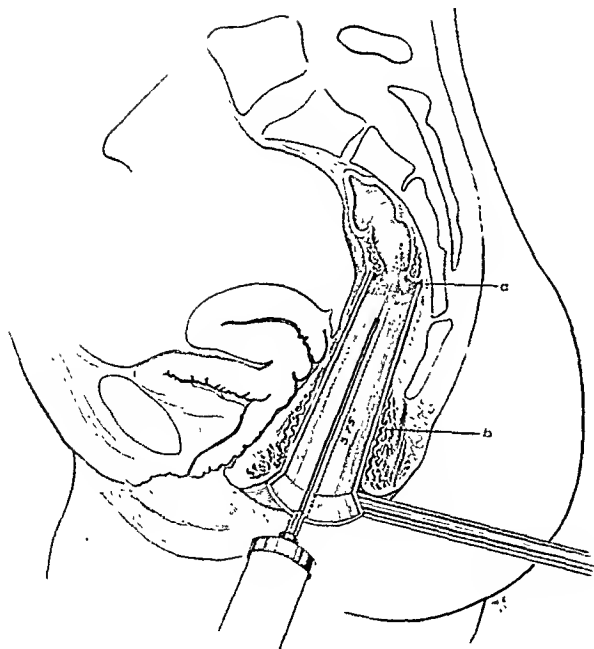


Fig. 1

rectum. Continual extrusion of these internal haemorrhoids through the anal canal results in stretching and impairment of the tone of the sphincter muscles and the haemorrhoids may remain continuously outside or require frequent reduction especially after bowel movements.

If one now inserts the proctoscope a little higher into the rectum above the low rectal varices, one will encounter a degree of mucosal redundancy, which in certain cases is quite marked, and may rise high up into the ampulla of the rectum crowding this area, especially in the anterior and lateral quadrants. This superfluous mucous membrane has an unhealthy, granular, edematous appearance. It is continually being dragged upon by the varices which it overlies and above which it rises into the rectum. Prolapse and strangulation may now supervene at any time. This accident really occurs, when not only the haemorrhoids, but the mucous membrane redundancy, already described, descends outside and reduction is not immediately effected. Certain cases present only the haemorrhoidal lesion (varices) with very slight mucous membrane redundancy, but in a group of cases this mucous membrane lesion is marked and well established. On the other hand, the varices may be quite small with the mucous membrane lesion as the outstanding feature. It is this latter type of case that may not present any signs or symptoms until the sudden extrusion of the redundancy occurs and which may be erroneously described as haemorrhoids. This occurs when for some reason sphincter tone is reduced in effectiveness *e.g.*, after certain fistulae operations, after parturition, in the aged, in the acute febrile states and in wasting diseases. Straining for any reason favours extrusion of the mucous membrane redundancy. In children, mucosal prolapse occurs following faulty bowel habits with straining, when after a time a redundant condition of the mucosa becomes established with its consequent extrusion. In children, the comparative straightness of the rectum and sig-

Fig. 1. (a) Demonstrates the height of the mucosal redundancy associated with internal haemorrhoids. The redundancy prolapsing into the lumen of the proctoscope is being injected with the sclerosing solution. The Author's proctoscope (rectoscope) measures  $3\frac{3}{4}$  inches in length and is especially constructed to reach above the prolapse in the ampulla recti.

(b) Demonstrates the level of the haemorrhoidal lesion in the lower rectum. The redundant mucous membrane covers the haemorrhoidal varices and rises into the ampulla recti. the varices have been flattened by the passage of the instrument over them.

moid with the flatness of the sacrum further favour the descent of the mucosal redundancy. Here, one is dealing with a pure mucous membrane prolapse, without rectal varices or at the most, very small ones.

One may now summarize by concluding that internal haemorrhoids are associated with a degree of mucosal redundancy, which in certain cases may be quite marked and assume the proportions of a mucous membrane prolapse. It is the recognition of the association of the mucous membrane lesion with internal haemorrhoids, which forms the basis of this paper.

#### SUBMUCOUS INJECTIONS WITHOUT OPERATION

Several submucous injections of five per cent phenol in sweet almond oil, administered at weekly intervals high up into the mucous membrane redundancy, should be tried in such cases where the mucosal lesion already described is found accompanying the haemorrhoidal varices. Submucous induration results in the obliteration of the mucous membrane redundancy, which, in itself, often is responsible for much of the protrusion complained of by the patient. The redundant mucous membrane is pulled up, so to speak, by this reaction, and the varices become surrounded by the submucous indurative process, which soon results in their obliteration. The lower rectum should be theoretically divided into four quadrants and injected at weekly intervals. The dose is from three to ten c.c. depending upon the degree of mucosal superfluity present. Cases which present free rectal bleeding should certainly be treated by this method, before subjecting the patient to surgical interference. Marked anaemia often results in such cases, even when the bleeding has not been excessive in amount (1) (4). One or two submucous injections usually will completely arrest the blood loss. The administration of a high iron diet subsequently should be ordered, together with iron ammonium citrate or one of the Bland and copper preparations (1).

The redundant mucosa overlying the haemorrhoidal varices has an unhealthy edematous granular appearance and this condition is often observed for a distance of one or two inches above the haemorrhoidal area extending into the ampulla of the rectum. This condition could really be described as a proctitis accompanying the haemorrhoidal lesion. After several submucous injections, the redundancy becomes obliterated and the mucous membrane after a month or six weeks, takes on a much healthier appearance and, in fact, seems quite normal. In many cases, the haemorrhoids are practically cured or considerably reduced in size. Bleeding from the haemorrhoidal area is nearly always arrested by this technique.



## SUBMUCOUS INJECTIONS FOLLOWED BY THE LIGATURE OPERATION

In a high percentage of patients suffering from internal haemorrhoids, the treatment by submucous injections will suffice to effect complete control of signs and symptoms. The prolapse will no longer be extruded, bleeding will be arrested and the patient will feel quite comfortable. Clinically this picture may be regarded as a cure. After a few months it may become necessary to reinject one of the quadrants. This is usually sufficient; and patients have been followed who after several years have had no recurrence and who have shown no untoward effects resulting from the treatment.

Sometimes it is difficult to determine beforehand which cases must be rejected for this ambulant type of treatment. The degree or size of the prolapse is no criterion. A loose patulous sphincter, epithelialization of the base of the prolapse (from long-continued extrusion), bad rectoceles in which the perineal body is deficient, are definite contraindications to the injection treatment. In cases where fissure, fistulae, large hypertrophied papillae or other accompanying ano-rectal lesions are present, one does not attempt treatment by the injection method. Age is unimportant and old people respond remarkably well.

There are certain patients who have a large degree of prolapse, and in whom the only type of operation which could be employed would be the Whitehead procedure. The bad after-effects of this type of operation have been frequently observed and recorded. A preliminary course of injections will often convert such a case into quite a simple one. After three or four large injections, the whole prolapse will be pulled up and fixed in the ampulla, where the submucous indurative process practically obliterates the redundancy with any underlying varices. All that may now have to be done, is simple undercutting and ligature of one or two remaining varices, (covered by mucous membrane), low down which still continue to be protruded, and which will not be controlled by submucous injections. The case which would therefore have required a formidable amputation or Whitehead type of operation either is completely relieved, requiring no further interference, or converted into one requiring a simple ligature procedure.

In those patients who show a marked anaemia as the result of the bleeding varices, a course of preliminary injections completely arrests the blood loss. Should operation be subsequently decided upon, one can do so at one's leisure and meantime employ appropriate diet and drugs for the anaemia. The risk of operating upon an anaemic patient, whose forces of resistance are depleted, is thus avoided.

The *ligature operation* referred to in this paper consists as follows:

Low spinal anaesthesia is induced with 50 mgms. of novacaine or 0.4 to 0.5 c.c. of a ten per cent solution of stovaine and sodium chloride in distilled water. (The

latter is employed at St. Mark's Hospital, London). The stovaine solution because of its high specific gravity of 1080 (cerebro-spinal fluid has a specific gravity of approximately 1007) gives a restricted zone of perineal and low rectal anaesthesia, eminently suited for operations upon the rectum.

The three primary haemorrhoids, usually a left lateral, a right anterior and a right posterior, each is individually grasped with Spencer-Wells forceps and pulled down outside the external sphincter, which is now completely relaxed. The muco-cutaneous border is now undercut with a pair of Mayo scissors, and the haemorrhoid whilst it is gently pulled down is undercut for a short distance. This distance is usually up to the level of the anal canal with the pile under traction in the prolapsed position. The base of the haemorrhoid is now transfixed with No. 1 chromic gut, on a curved needle, passed through the center of the haemorrhoidal mass and the ligature thus firmly tied. The redundant part of the haemorrhoid is snipped off and the remainder will later slough out with the ligature. Each haemorrhoid is thus individually dealt with. A light vaseline packing is inserted in place at the completion of the operation.

This type of operation employed at St. Mark's Hospital for Rectal Diseases in London, is simple, satisfactory and gives excellent results. Submucous injections of phenol in oil are extensively used at that hospital in a high percentage of cases of internal haemorrhoids, and by Gabriel in practically all cases of rectal prolapse (3). A great number of surgeons employ the ligature operation today for internal haemorrhoids.

## SUMMARY AND CONCLUSIONS

The mucous membrane lesion in internal haemorrhoids is recognized and described. The relationship

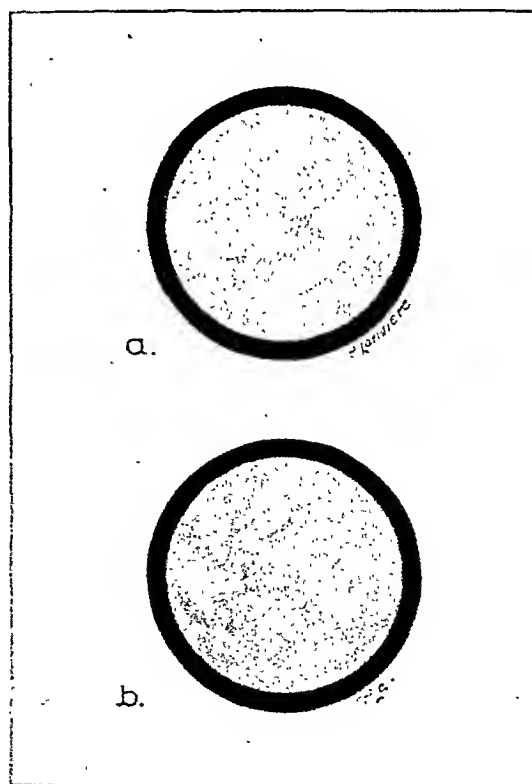


Fig. 2. (a) Demonstrates view through end of proctoscope inserted full length. The mucosal redundancy can be seen prolapsing into the lumen of the instrument. (b) Demonstrates the haemorrhoids prolapsing into the lumen of the proctoscope in the lower rectum. The instrument has been withdrawn to (b) Fig. 1, below the area of prolapse. Note the difference in level between (a) and (b).

between mucous membrane prolapse of the rectum and internal haemorrhoids is studied.

The value of submucous injections of five per cent phenol in almond oil into the redundant mucous membrane in cases of internal haemorrhoids has been pointed out.

In cases of mucous membrane prolapse of the rectum such formidable and unsatisfactory operations as the Whitehead, and amputation of the prolapse have become unnecessary with this plan of treatment. Operative interference is often altogether avoided by employing the treatment outlined. This treatment is ambulant in nature and the patient does not have to be hospitalized or his activities curtailed. (In complete rectal prolapse in adults, Gabriel employs submucous injections of five per cent phenol in almond oil, together with para-rectal injections of a solution of quinine sulphate and dilute sulphuric acid in distilled water; the patient is hospitalized). His results in complete prolapse have been very satisfactory with this method, which he prefers to any type of operation (3). The treatment by submucous injections,

with modifications, (smaller dosage) is satisfactory in the type of prolapse often seen in children, which lesion does not respond to simpler measures.

This procedure is very useful in those patients with internal haemorrhoids who show secondary anaemia. The risk of operating upon an anaemic patient is thus avoided.

The ligature operation is described as a simple and satisfactory procedure in dealing with those cases of internal haemorrhoids that do not respond to the injection technique or where such is contraindicated.

#### REFERENCES

1. Daniels, E. A.: Rectal Haemorrhage. *Canad. M. Assoc. J.*, 33:287, 1935.
2. Daniels, E. A.: Early Diagnosis in Rectal Cancer and Prognosis on the Basis of Duke's Classification. *Canad. M. Assoc. J.*, 31:612, 1934.
3. Gabriel, W. B.: The Principles and Practice of Rectal Surgery. 1st. ed., H. K. Lewis & Co., London, 1932.
4. Daniels, E. A., Fundamentals in Rectal Diagnosis. *Canad. M. Assoc. J.*, 31:289, 1934.
5. Daniels, E. A.: Disturbances Produced in the Rectum by Disease Elsewhere. *Canad. M. Assoc. J.*, 28:499, 1933.
6. Daniels, E. A.: The Ano-Rectum in Chronic Constipation. Ready for publication in *Canad. M. Assoc. J.*

## SECTION VIII—*Editorial*

*NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastroenterological Association is in no way responsible for editorial expressions.*

### ON THE PROPOSED "INSTITUTE FOR GASTRO-ENTEROLOGICAL RESEARCH"

**A**FTER reading the presidential address of Dr. B. B. Vincent Lyon delivered before the American Gastro-Enterological Association last June, published in the October, 1935, issue of this Journal, we feel that the suggestion contained therein, as to the need for establishing a Research Foundation devoted exclusively to the study of the manifold unsolved problems connected with various gastrointestinal and metabolic diseases, is a most worthy one. We feel that it should have whole-hearted support, not alone of the members of the American Gastro-Enterological Association but from all members of our profession who recognize the timeliness of Dr. Lyon's suggestions. It is hardly necessary to call attention to the great need for such a concerted attack upon the day-by-day problems that confront the clinician or specialist interested in the field of gastroenterological medicine and surgery.

Dr. Howard F. Shattuck of New York, on assuming the 1935-1936 Presidency of the American Gastro-Enterological Association, appointed Dr. Lyon, Chairman of the Research Fund Committee and the latter, in turn, appointed the following doctors to serve with him:

#### GENERAL COMMITTEE

Aaron, Abraham H., Buffalo.  
 Abell, Irvin, Louisville.  
 Alvarez, Walter, Rochester, Minn.  
 Andresen, A. F. R., Brooklyn.  
 Barborka, C., Chicago.  
 Bastedo, Walter A., New York.  
 Bloch, Leon, Chicago.  
 Blackford, John Minor, Seattle.

Bockus, Harry L., Philadelphia.  
 Boles, Russell S., Philadelphia.  
 Brooks, Harlow, New York.  
 Brown, Ralph, Chicago.  
 Brown, Thos. R., Baltimore, Md.  
 Cheney, Wm. F., San Francisco.  
 Clasen, Arthur C., Kansas City.  
 Corbus, Burton R., Grand Rapids.  
 Cornell, Beaumont S., Fort Wayne.  
 Crohn, Burrill B., New York.  
 Dowden, C. W., Louisville.  
 Eggleston, Elmer L., Battle Creek.  
 Eusterman, Geo. B., Rochester, Minn.  
 Friedenwald, Julius, Baltimore.  
 Gorham, Frank D., St. Louis.  
 Harris, Seale, Birmingham.  
 Heyd, Chas. G., New York.  
 Ivy, A. C., Chicago.  
 Jones, Clement R., Pittsburgh.  
 Jones, N. W., Portland, Oregon.  
 Jordan, Sara M., Boston.  
 Lahey, Frank H., Boston.  
 Lyon, B. B. Vincent, Philadelphia.  
 Martin, Lay, Baltimore, Md.  
 Mateer, J. G., Detroit.  
 Miller, T. Grier, Philadelphia.  
 Morgan, Wm. Gerry, Washington.  
 Piersol, Geo. M., Philadelphia.  
 Pilcher, Jas. T., Brooklyn.  
 Portis, Milton, Chicago.  
 Rehfuess, Martin E., Philadelphia.  
 Sachs, Adolf, Omaha.  
 Sawyer, John P., Cleveland.

Schiff, Leon, Cincinnati.  
 Shattuck, Howard F., New York.  
 Simon, Sidney, New Orleans.  
 Smithies, Frank, Chicago.  
 Soper, Horace W., St. Louis.  
 Swalm, William A., Philadelphia.  
 Verbrycke, J. Russell, Washington.  
 White, Franklin W., Boston.  
 Zerfas, L. G., Indianapolis.

#### EXECUTIVE COMMITTEE

Andresen, Albert F. R., Brooklyn.  
 Bastedo, Walter A., New York.  
 Boles, Russell S., Philadelphia.  
 Bockus, Harry L., Philadelphia.  
 Brooks, Harlow, New York.  
 Brown, Thos. R., Baltimore, Md.  
 Crohn, Burrill B., New York.  
 Friedenwald, Julius, Baltimore.  
 Jordan, Sara, Boston.  
 Lyon, B. B. Vincent, Philadelphia (Chairman).  
 Martin, Lay, Baltimore, Md.  
 Miller, T. Grier, Philadelphia.  
 Morgan, Wm. Gerry, Washington.  
 Piersol, Geo. M., Philadelphia.  
 Pilcher, Jas. T., Brooklyn.  
 Reh fuss, Martin E., Philadelphia.  
 Shattuck, Howard F., New York (Chairman  
 Ex-officio).

Smithies, Frank, Chicago.  
 Verbrycke, J. Russell, Washington.

It is probable that distinguished clinicians and gastroenterologists not themselves members of the American Gastro-Enterological Association will be requested to serve on the General as well as on the Executive Committee.

The Fund to be raised should be five million dollars—certainly not less than three and a half million dollars—if the income alone is to be made use of, taking 3% as the maximum safest income-producing figure. If all or a portion of the principal can be spent during the life time of the Research, a lesser sum would be required.

We fully endorse Dr. Lyon's suggestion that any individual doctor who submits an idea for research which finally proves successful, should then receive as large a degree of credit as does the Research Staff which actually has done the technical work.

Already the Committee has been approached by several well-known promotion firms, who have requested that their services be made use of in the raising of this Foundation Fund. The charges for services of these firms vary between 6 to 12% of the amount of the fund raised. These promoters have elaborate plans, such as team captains, luncheons and dinners customary to such a campaign.

The Committee feels that such outside "professional" help should not be engaged until we, ourselves—the American Gastro-Enterological Association, its Committee and its medical friends—have exhausted the list of possible donors and have failed to reach the objective.

The Committee, therefore, hopes that each member of the American Gastro-Enterological Association or any clinician or specialist in diseases of digestion and nutrition or any individual interested in the successful

promotion of this worthwhile cause will communicate to the Committee the names of any philanthropically inclined person or persons who might desire or be induced to donate the entire Foundation or contribute a portion of it. When names of possible donors are forwarded, it would aid the Committee if proposers would offer their suggestions as to how such prospects best can be approached.

If the goal is to be reached, certainly, it is necessary that each of us who feels that such a Research Foundation as advanced by Dr. Lyon eventually would yield large dividends to the public, should get behind this movement and help consummate the plan. Recent acts of the Government in respect large fortunes make the time propitious for the possessors of wealth to avoid extraordinary demands in the form of taxes. How much more satisfactory it would be to individuals controlling large funds if they contributed generously of their means to a Foundation which not alone would perpetuate their families' names but at the same time, would be of far more service to humanity than if the ever-reaching tax collector forced their funds into a bottomless bin whose contents fed innumerable dubious, often politically-controlled, projects!

Reader, put *your* shoulder to the wheel and do not leave this worthy—and admittedly difficult—task wholly to the efforts of Dr. Lyon and a few of the "ever-faithful." Surely, some of the 130 members of the American Gastro-Enterological Association have contacts with men of large fortunes, of such nature, that when the character of the proposed Research Foundation is explained, they will respond generously—and promptly.

There is a big job ahead. Let's do it!

Frank Smithies.

#### PROCTOLOGY, A SPECIALTY, AND ITS INFLUENCE UPON THIS JOURNAL'S PUBLICATION POLICY

**D**URING the past two decades no diagnostic and surgical specialty has more thoroughly earned its right to serious consideration than has Proctology. Progress, too, has been made against most discouraging handicaps.

Within the memory of most of us, time was when certain lazy or a bit "off color" members of our craft, recognizing the anatomic limitations to patients directly inspecting their own anal sphincters and some twenty inches of cephalad bowel, thus determining how little or how much—especially how *little!*—ailed them, quite shrewdly appraised therein the possibilities for lucrative "business." Learnedly these practitioners dubbed themselves "proctologists." Living strictly up to the Greek roots, from which this word directly is derived, these pioneering lads "talked about the anus" long and oft. However, in "professional" activities, they *transposed* the zoölogic meaning of their specialty's name, so that (as in *fish*—of which they had many in their practices!) "*proctos*" became "the fin (theirs!) in *front* of the *vent*," rather than "the vent in front of the fin!"

That the "specialty" proved profitable, soon was demonstrated. Not alone was there a rapid increase of the proctologic clan but, before long, every city of importance harbored its nests of proctologic quacks who displayed—in newspapers or by electric signs—

their blatant advertisements. Indeed, to the layman, particularly the ordinary working man, the word "specialist" grew to signify one who either chased the festive "biscuit-boys" or who sadistically titillated the ever-vibrant sphincter ani.

Without full appreciation of the degree of popular and professional prejudice which obstructed them, it is not possible to credit the modern proctologist sufficiently for the broad strides forward which actually he has made. To be sure, yet we have abroad in the land numerous generous-paunched, pink-cheeked, old womanish, breezy, loquacious "Docs" (often boasting also several sub-titles, "earned" from cultist, self-styled "colleges") who possess such eagle eyes that they locate—and *treat endlessly*—lesions which only they and God can see, by means of tubes, syringes, tiny needles, bits of thread, the "radio-knife," smelly ointments, "lights," the "modalities," etc., etc. Usually, they "hold" their victims by claiming to be keeping them just a few hops ahead of cancer: missing a single treatment means having the "awful spectre" spring forward! These pathetic specimens of practitioner, ignorant or knowingly dishonest, make mountains out of mole-hills, botch the management of actual lesions or, all too often, wholly fail to recognize, not to mention, treat, true malignancy, serious infection, fistulae, parasitic invasion, organic nervous disease or frank psycho-neuroses. They are a menace to patient and profession alike: they have made most difficult the advance of the skilled specialist.

It has followed then, that in the "rehabilitation" of proctology—indeed in the proving it to be an *essential specialty*—the most important progress made by today's proctologists has been that concerned with the accurate *diagnosis* of affections which could be established in no way other than by intelligent, direct inspection of the parts involved. One need but linger a day in the Proctologic Clinic of a reputable institution, staffed by trained and skillful men, to realize that their's is a specialty. He will learn that to them diagnosis is something far beyond what is conceived by the internist or surgeon and, certainly, incomparably more than what the occasional, peeper-through-a-proctoscope ever imagined. The modern proctologist begins his diagnostic study where the general surgeon, the internist or even the gastroenterologist, believes it has been completed.

Our ranking proctologists have become experts in a most essential and specialized field of pathology. This should be recognized and appropriate credit given. When one stops and thinks, he becomes aware that proctologists have given us special, diagnostic information quite comparable in value with that advanced by the urologist, the cardiologist, the rhinologyngologist, the thoracic surgeon. We should recognize that it is to proctologists that we owe the recognition of early amebic infection, the classical superficial pathology of chronic ulcerative colitis, the descriptions of low-lying tuberculous and luetic lesions, the discovery of early malignant disease, the location and the significance of polypoid growths, the "cord rectum," the various neuroses affecting—often in association with obscure pain—the sigmoid and rectum, the accurate appraisal of strictures and of fistulous tracts and, within the past few years, the pathology of lymphogranulomata. Proctology now means more than "piles" and "fissures," yet, undoubt-

edly, if one be himself a host to such pathology, the proctologist more accurately recognizes the location, nature and extent of these annoyances than can men who have not given special consideration to their origin, course and pathologic variations.

In *differential diagnosis*, the competent proctologist is capable of furnishing valuable information by returning reports of a *negative* character. In instances of bleeding from the bowel, in this book it should not be necessary to emphasize the worth, to the internist or the surgeon, diagnostically, of the proctologist's assuring him that the source of the bleeding lies *not* in the lower colon segments. Clinically, all too often, failure definitely to exclude the sigmoid, rectum and anus as *loci* of bleeding lesions, leads to haphazard, and unsuccessful, therapy. Further, from no specialized diagnostician other than the trained proctologist can information be obtained regarding the progression or cure of local, lower bowel disease. At no hands other than his, can one secure representative smears, scrapings or specimens of tissue for biopsy. Often, indeed, the proctologist, experienced in recognizing gross pathology within his field, can render a correct diagnosis long before smears and tissue-bits have been subjected to laboratory examination.

Those not familiar with the work in modern proctologic clinics make themselves ridiculous when they scoff at the specialty. Unfortunately, many of even our so-called prominent surgeons or internists never have visited a properly-staffed clinic for proctologic diagnosis. In fact, in many cities which style themselves "great medical centers," proctologic clinics actually do not exist. Rarely do medical students see a gut through the proctoscope; when they do, it is more than likely that those who are "instructing" them know little of what is seen. Indeed, many of our large hospitals do not even possess proper examining-tables and, certainly, few of them or their dispensaries can boast of down-to-date instruments or of men capable of using them. From such cities and institutions come the loudest outcries against the specialty, proctology. Sad, it is for patients who appear for diagnosis, that many critics hold positions in which it is taken for granted that their holding them, guarantees familiarity with all helpful, modern diagnostic procedures and that they will see to it that nothing is neglected which will elucidate the problems created by disease. While the patients put their trust in such don't-know-that-they-don't-know type of "chief," available scientific knowledge goes a-begging and disease which, if recognized early is curable, passes on to the hopeless stages.

*Surgically*, unquestioned advances have been made. One has but to see a patient in the old-fashioned, lithotomy position, under general anaesthesia or with pain incompletely deadened by insufficient "local" anaesthetics, having his "piles" removed (?) by the ancient, "clamp-and-cautery" method, by "blind" incisions or by the destructive Whitehead operation, to realize the beneficent surgery the proctologist has made possible by his leisurely, always visible, thorough dissection of each hemorrhoidal mass under spinal anaesthesia—and at no risk and with no distressing after-course to the patient. Ask the subject who is experiencing surgery for relief of hemorrhoids which have recurred, *subsequent* to operation by "the clamp-and-cautery" or the old ligature methods, whether modern proctologic surgery warrants recognition as a

specialty! Should a member of our own profession acquire hemorrhoids, if he is at all informed, his choice of operator is the modern proctologic surgeon, if he can reach him.

Dozens of surgical or non-surgical methods of treatment have made management of anal and lower colon affections surer and less distressing as a result of specialization. That these therapeutic advances *generally* are not known or understood, largely is due to there being relatively so few modern proctologic clinics and because, where such clinics do exist, physicians fail to visit them and acquire first-hand knowledge. Is it to be wondered that while an eminent surgeon may perform partial gastrectomy brilliantly, he fails lamentably in the presence of rectal stricture or fistula? Yet, seldom does he resist tackling such; rarely has he the courage to admit his limitations and insist that patients place themselves in the hands of men, to whom the operative field is familiar ground, and surgery there is easy, quick, painless and satisfactory.

The writer feels that proctology has earned its "place in the sun" and should be allowed to occupy that place. This Journal, from its inception, has given space to articles from leading proctologists. It plans to enlarge that space. Through the courtesy of its Executive Officers, arrangements have been made

whereby such papers as annually are presented before the American Proctologic Society and have been approved by the Organization's Publications' Committee will appear in this magazine. Further, it is proposed to print that most commendable feature of the Society's activities, the Annual Abstract of Literature as compiled by one of its members.

The current year's "Abstracts" have been made by Dr. Clement L. Martin, Chicago. A tedious task is the preparing of an annual abstract of the literature of any special topic, but when carefully done, the results are invaluable to those concerned. Dr. Martin's "Abstract" represents a most conscientious effort to visibilize proctologic advances as they are revealed by the World's literature. Apart from its value to proctologists, this feature, of itself, should assist greatly the general surgeon and the internist to a realization of what real progress is being made by trained, earnest proctologists every where and should teach much to those of our profession who are yet capable of being taught and are willing to learn. Its publication may induce certain "die-hards" even to visit a modern clinic which is devoted to proctologic diagnosis and treatment!

Frank Smithies.

## ABSTRACTS

### GENERAL

In detailing the "Progress in Rectal Surgery" Gordon-Watson emphasizes the following:

The mechanics of the operation for fistula in ano remain about the same as they are in the 14th Century as practised by John Arderne. He believes he has evidence to prove that fistula in ano arises in ano-rectal glands which probably represent mucous glands of the primitive cloaca which persist in some adults and communicate with the anal canal.

Much progress has been made in treatment of Cancer of the Rectum and sigmoid in the last 25 years. He mentions the Miles and Lockhart-Mummery operations.

He associates rectal adenomata and cancer very closely. He believes that the sequence: hyperplasia, adenoma, cancer, is "clear cut and established" on the basis of the work of Dukes. As a cancer progresses any associated adenomata seem to be inhibited and regress.

The mortality following colostomy has been reduced from 69% in 1869-78 (lumbar) to 9% (on a five year average) at present.

He notes that the explanation of vesico-colic-fistula on a basis of diverticulosis was not made until present century. Recto-sigmoidectomy is advocated for prolapse and presacral sympathectomy for megacolon.

Daniels reviews the fundamentals in rectal diagnosis. He requires a simple history considering tuberculous infection and the use of alcohol. There should be a careful examination including palpation of perianal, anal, and rectal regions, and careful inspection with and without instruments. Every patient should be sigmoidoscoped and multiple lesions looked for, especially adenomata and carcinomata. The differential diagnosis of fissure in ano, tuberculous anal ulcer, chancre of anus, and epithelioma of anus is important.

Durst directs attention to the proper use of the proctoscope, noting among other points that digital examination

should precede the use of the instrument, that the proctoscope should be passed without the use of air inflation if possible, that it should not be advanced until the bowel is well seen and the direction of the lumen noted.

Gabriel enumerates the following as the recent advances in the treatment of rectal diseases: low spinal anesthesia, dettol (a new antiseptic), surgical diathermy, sclerosing substances in the treatment of hemorrhoids and prolapse, anesthetics in oil, recto-sigmoidectomy for prolapse, Frei test in rectal stricture, perineo-abdominal excision for cancer, presacral sympathectomy, intraspinal injection of alcohol for pain, sigmoidoscope with proximal light, and diathermy forceps.

Goldberger (1) states: While using the ordinary proctoscope one gets only a diagonal or oblique picture of the field and the view is never larger than the transverse section of the tube.

There are three faults of the ordinary proctoscope:

1. An exact and correct view may only be obtained while withdrawing the proctoscope and the viewpoint is limited.

2. Fecal masses are difficult to circumvent and sometimes can not be passed at all.

3. Sharp turns, ulcerative processes, distant strictures and stenoses are serious hazards.

With this in view the Author has constructed a new instrument which may be introduced higher in the colon and shows a larger and better field, magnified if necessary.

This new instrument is called the Diapetan Rektoskop.

It permits inspection of the bowel with air or water and is similar to the cystoscope. The light can be turned so the side walls can be seen or may be turned so the inspection is forward. This new Rektoskop is very narrow measuring 12 m.m. in diameter and carries at its point a high powered lamp. The inner part of the tube is divided

1. Goldberger, J.: Endoscopy of rectum and sigmoid with new method of unfolding organ. *Med. Klin.*, Berlin, 30:738 (June 1) 1934.

into two portions for the inflow and return of the water. The tube also has a handle to operate the light carrier and may be turned 360°.

### HEMORRHOIDS

The indications and limitations of injection procedures are becoming more generally known and on the other hand it is perhaps more generally recognized that not every patient having hemorrhoids necessarily requires an operation. Kleckner's article is a concise sound consideration of the subject, as are Cartwright's and Silvers'; Hayes discusses the important factors in minimizing post-operative pain.

Discussion of the Whitehead operation continues, chiefly in foreign journals.

Two books have been brought out on the subject in the last year, one by McAusland, the other by McNamara.

### FECAL IMPACTION

Norbury reports the case of a mentally defective girl 18 years of age who had an operation soon after birth for

imperforate anus with recto-vaginal fistula. At 16 years of age she had a very large fecal impaction extending up to the umbilicus which was broken up manually under anesthesia and the bowel cleared by enemas. Two years later the condition recurred but relief was not successful by the same method and the patient died several weeks after the attempt to relieve the impaction under anesthesia. Necropsy showed fecal impaction with the hypertrophied rectum measuring 9 inches in diameter and the colon 5 inches in diameter. The thoracic contents were pushed up and compressed by the diaphragm which rose high into the abdomen. "Supposed cause of death--Asphyxia and syncope."

### FECAL IMPACTION

Stewart and Illick cite a case of obstruction from four large fecaliths and show in their article an excellent reproduction of the roentgenogram.

Dr. Clement L. Martin, Chicago, Illinois.

## SECTION IX—Book Reviews

(This section is open to contributions from any medical reader, whether or not a member of the Editorial Council).

*Vegetables and Their Significance in the Physiology of Digestion.* An experimental and Clinical Study by Dr. N. T. Leporsky, Professor of Medicine, University of Voronej. 345 pp. (Russian), Voronej, U.S.S.R., 1934.

THE ancients attributed great importance to a vegetable diet. They not only ascribed to it nutritive properties but successfully used many vegetables as curative and preventive agents in disease. However, the advances of modern chemistry gave ground for the belief that proteins, carbohydrates and fats are the basic foods, whereas vegetables, having a low caloric value, were regarded, till recently, as auxiliary foods of gustatory and not of nutritive importance. This may explain why, along with fundamental physiological investigations concerning the effect of proteins, carbohydrates and fats on digestion, there had been no similar study of the rôle of vegetables.

The discovery of vitamins, however, revealed the importance of vegetable foods in the diet. About the same time, the investigation of the effect of vegetables on digestion was begun in Professor I. P. Pavlov's laboratory. In the book under discussion, the Author summarizes the results of his seventeen years' experience along the lines of the work which he began in Professor Pavlov's laboratory. His experiments on animals are supplemented by clinical observations on patients and healthy individuals. Numerous protocols, diagrams (37) and tables (125) included in the text illustrate the exhaustiveness of the study and give a clear conception of the technique employed. The book is a valuable contribution to the physiology of the gastro-intestinal tract. It also contains many data useful to the gastro-enterologist and to the general practitioner. The following vegetables and their juices, and soups and *purées*, also fractional extracts, prepared from them, were employed: cabbage, beet, radish, turnip, cucumber, lettuce (*Lactuca sativa*), carrots, as well as mushrooms.

Beginning with the buccal cavity, it is shown that, regardless of the mode of preparation, vegetables provoke a greater salivary secretion than do meat, bread or milk. The effect of vegetable juices, soups and other preparations on the gastric secretion is still more pronounced. All kinds of vegetables, whether cooked or raw, are shown to activate a far greater secretion of gastric juice than extracts of meat (3.0 per cent) and fish. It is shown that vegetables and their juices act as chemical exciting agents which provoke an early "second phase" of gastric secretion. Unlike other chemical agents, such as meat extract, vegetables provoke a secretion exclusively by coming into contact with the mucous membrane of the pyloric part of the stomach and are ineffective when introduced into the intestine. Secretion commences soon after the administration of the vegetable food (the latent period not exceeding 45 minutes), rapidly reaches its height and remains abundant, lasting usually about two hours. The gastric juice obtained under these conditions is of high acidity and digestive power. A detailed analysis revealed that raw vegetables and their juices produce a comparatively greater secretion than do cooked or dried vegetables. Soups prepared from fresh vegetables are more active than are those prepared from dried vegetables. Salted and pickled vegetables, however, exhibit a very pronounced effect, but this must be ascribed to the addition of salt, vinegar and spices and not to the properties of the vegetables themselves. Experiments with different fruits and their juices gave similar results; these may be included in the same category as vegetables.

The addition of vegetable juices to meat extracts increased the secretory effect of the latter by 200 to 300 per cent. When meat and vegetables are administered together, the amount of gastric secretion is greater than is the sum of the secretions produced when meat and vegetables are given separately. The explanation lies in the fact that the addition of vege-



tables facilitates the digestion of meat and that during the process of digestion of the meat products are formed which are themselves "activators" of still further secretion of gastric juice.

The addition of vegetables to carbohydrate foods has a very similar effect to that produced on the digestion of proteins mentioned above: the secretion of gastric juice is much greater than when carbohydrates are administered alone and also it is greater than the sum of the secretions obtained when carbohydrates and vegetables are given separately. The secretion provoked by bread, potatoes and other carbohydrate foods is chiefly of a reflex nature, the chemical phase being insignificant. In view of this fact, the addition of vegetables to carbohydrates is of special importance in cases in which the "first phase" of gastric secretion is excluded (as happens, for example, with loss of appetite or in hurried eating of unpalatable food). The increase in the volume of the secretion in these cases amounted, under experimental conditions, to as much as 520 per cent.

The conditions become more complicated when vegetables are combined with fats. As is known, fats at first inhibit gastric secretion, and it is only after they are converted into soaps that they act presumably as secretagogues. The addition of vegetable juices to a fatty diet provokes a long continued secretion of gastric juice. It reaches its maximum in the first hour, which means that the vegetables are capable of counteracting the inhibitory effect of the fats. On the whole, the period of secretion activated by a combination of vegetables and fats is only slightly longer than when fats are administered alone, but the *total* amount of gastric juice secreted is greater (up to 100 per cent) and the juice is more acid and of higher peptic power.

The effect of vegetables on the pancreatic secretion also was studied. Concentrated vegetable juices and soups under normal conditions were found to inhibit pancreatic secretion, but when diluted from five to ten times the same agents activated secretion. The more strongly a concentrated vegetable juice inhibited the pancreatic secretion, the more powerfully did it stimulate when diluted. This was found to be true, also, as regards the duration of the secretion, as well as the digestive power of the pancreatic juice. With slight variations these conditions were shown to hold both in dog and man.

It is interesting to note that, in patients exhibiting achylia gastrica, the conditions were found to be reversed: thus, concentrated vegetable juices stimulated the pancreatic secretion, whereas diluted they had an inhibitory effect. Also, the content of enzymes was found to be higher in the pancreatic juice of patients who exhibited achylia gastrica.

Concerning the influence of vegetables on the secretion of bile and its discharge into the duodenum, it is shown that, for about three hours after the ingestion of a vegetable meal, the *secretion* of bile is doubled. Concentrated vegetable juices administered by themselves or along with proteins and carbohydrates inhibited the *discharge* of bile into the duodenum. However, when taken with fats they increased the discharge of bile into the duodenum by 50 per cent. When diluted ten times, the vegetable juices acted by themselves as powerful cholagogues and were success-

fully used by the Author in duodenal intubations for the treatment of cases of angiocholitis.

These observations led the Author to infer that vegetables act not only on the glandular apparatus of the gastro-intestinal tract but also on its neuromuscular apparatus. This view is substantiated by an experiment in which the administration of 300 c.c. of a salt-containing fraction of vegetable juice to an animal quickly precipitated defecation.

In an attempted analysis of the active principle of the vegetables studied, the Author comes to the conclusion that the salt-containing fractions are the most active, whereas other fractions grow less potent in proportion to the decrease of the concentration of salts in them. The vitamin content of various vegetables and preparations made from them received little attention in this investigation. Therefore no definite conclusions in regard to the nature of the secretagogue substances present in the vegetables can be made.

The last chapters of the book contain a brief discussion of the application of vegetables in the treatment of various gastro-intestinal ailments. Vegetables are considered to be "regulatory" agents in the process of digestion. Their importance as stomachics, cholagogues and cholagogues is stressed and their use in gastric achylia is emphasized.

George W. Stavraky, Montreal, Canada.

*Child Psychiatry*, by Leo Kanner, M.D., Associate Professor of Psychiatry, The Johns Hopkins University, with prefaces by Adolph Meyers, M.D., L.L.D., and Edwards A. Park, M.D., of The Johns Hopkins University. 510 pages; published 1935 by Charles C. Thomas, Springfield, Ill., and Baltimore, Md., price \$6.00, postpaid.

NO aspect of pedagogy, particularly as applied to children and youth, is receiving greater attention by teachers of the first rank than is psychiatry and its application to the pupil in respect his capacity for receptiveness, his limitations, the *why* of those limitations and the topics suited best to him as influences towards the development of his future usefulness in business, the professions or, broadly considered, a member of our complex society.

In the Middle West, those interested are familiar with the excellent contributions upon Child Psychiatry from the viewpoint of the teacher which, during the past decade have emanated from such representative institutions as the School of Education (The University High School), University of Chicago and from the Francis W. Parker Private School. At these schools, for more than twenty years, genius, delinquency, low grade intelligence, exhibitionism, habits—all have been analyzed, not alone from the standpoint of the various formulae presumed to indicate natural ability, capacity or limitations to learning, but by cooperative clinical investigations by many persons. Of these persons, the physician, whether a psychiatrist, a pediatrician, a laboratory worker or a physical diagnostician, more and more, has served to elucidate pedagogical problems which had not been solved strictly from research into heredity, family, environment, study habits and the multitude of avenues so commonly explored previously by those interested in the art and the science of teaching.

Now comes from one so advantageously and uniquely placed as is Dr. Leo Kanner, a treatise titled "Child Psychiatry." In the reviewer's opinion, really this is a book most importantly concerned with pedagogy. It is not just a book but probably the most important book in its field which yet has been offered to teachers. While the work may not have been written with that object—it may have been meant for pediatricians, for aught we know!—our opinion is that no institution seriously interested in pedagogy, its true significance, the lines of its advancement and in the individual being taught, can afford not to take Dr. Kanner's book very much to heart. It should be read and analyzed through its every page and there should be adopted into every day practice the information imparted. In a large degree, such should shape programs for the investigation and the management of children and adolescents upon the basis of medico-psychiatric analyses and the deductions presented.

To the pediatrician, of course, these studies grouped from the extensive and carefully tabulated material at Johns Hopkins, are invaluable: that is, if appreciated. At present we still have too vast a horde of pediatricians to whom the specialty means little more than height-weight-age-sex-calories-diapers-food formulae-stools-bellyaches-exanthemata-running ears and noses and walking the floor at night! If the specialty, pediatrics, ever is to mean anything, in a broad sense, teaching it and practicing it along the lines set forth in Dr. Kanner's work are imperative. Otherwise, hospital waste-pails will continue brimfull of needlessly removed tonsils and adenoids, appendices, loops of gut, remnants of the newspaper-made-famous "upside-down" stomachs;—and parents and institutions will continue to be dizzied and bankrupted with alphabetically christened and numbered vitamins, hog-washes, "accepted" foods, pocket-book flattening organ-extracts and a thousand "new" agents supposed to rebuild, re-vivify and make lovely.

Space does not permit page-by-page review of Dr. Kanner's book: it is encyclopaedic, yet, withal, where "sampled" rather thoroughly, it appears not only complete but rational. The "light-reader" or "skipper" will find little comfort in this publication. Each page is packed with most substantial *pabulum* which requires leisurely digestion. Those who long have sought

a work from one in authority will adopt Dr. Kanner's book without questioning and come to regard it as one of the few "key" volumes in their libraries.

Of special interest to the readers of this Journal are the chapters dealing with "The Endocrinopathies," "The Digestive System," "Habitual Manipulations of the Body," "Faulty Feeding Habits" and "The Attack Disorders." As is the case with each section, these chapters exhibit a wide range of knowledge, proper perspective, balance, the avoidance of faddism and startling statements introduced for their effect upon the curious or the impressionable. Newer investigations in physiology (as the "conditioned reflexes" of Pavlov, etc.), neurology and anatomy are introduced in orderly fashion and where they form real contributions to the topic under discussion: they are not exhibited as mere evidence that the Author has "read up" and desires that his reader be aware of that fact. Excerpts are correctly and honestly credited; deductions are made from a background of well assimilated evidence. Indeed, the section dealing with digestive disorders, as manifested by children, sufficiently is adequate to warrant place in a treatise compiled by a gastroenterologist. It is refreshing to find such thorough consideration of so-called "specialism" in a book purporting to be but a general survey of a many-sided topic. No gastroenterologist can afford not to read and ponder over the sections being discussed: his diagnostic and therapeutic horizons will be widened—on right lines, too!

As is usual with a "Charles Thomas" publication, one finds Dr. Kanner's book properly, nay, elegantly, ordered and dressed. Binding, paper, type-fonts and index, all are attractive, complete and accurate (the index proved its worth on twenty-five random tests). It must be a source of great satisfaction to an Author who has labored diligently and intelligently to have the results of his efforts presented to the public in the "Thomas" way. To the reader, the publisher's nice custom of giving facts regarding the technical aspects of a book is both educational and unique. We like it. We are of the opinion that those who are concerned with the actual planning and building of a volume must derive a lot of pleasure from having set forth in summary the steps leading from manuscript to finished tome.

Frank Smithies.

## ABSTRACTS

RICHTER, H. M.

*Gastric Resection for Peptic Ulcer; Technique. S. G. O., Vol. LIX, No. 3, pp. 337-343, Sept., 1934.*

The Author presents his idea of the objective to be obtained in wide resection of the stomach for peptic ulcer, and gives a short description of the more important steps in technique. The objective, he states, is not to alter the acidity or alkalinity of the stomach or duodenum, but is to remove the ulcer bearing area of both the stomach and duodenum. Recurrence of ulcer is probably most frequently due to a failure to accomplish a sufficiently wide resection; certain technical errors such as

spur formation, badly arranged gastro-jejunal anastomosis, etc., probably play a part.

The operation described may be used as an emergency procedure within a short period after perforation, but usually there is adequate time to prepare the patient. Hemorrhage can usually be controlled by various measures, including, first and foremost, adequate blood transfusion. Severe starvation and dehydration may be corrected in part by the administration of water, salt and glucose, intravenously, hypodermically and rectally. The Levine nasal tube is passed the evening before operation in cases of retention, and is

allowed to stay in place; toward the end of the operation it is pushed down into the jejunum to facilitate early post-operative administration of liquids.

The choice of incisions is a personal one; each has certain advantages and disadvantages. After routine exploration the anterior surface of the stomach is grasped with two heavy forceps at two points along the long axis of the stomach. By using those forceps as handles the stomach is pulled down, and the bloodless gastro-hepatic omentum is pierced with two fingers. That maneuver allows the transverse colon to fall away from the stomach by admitting air into the lesser peritoneal

sac. The stomach is now raised, and the gastro-colic omentum is grasped in bunches between forceps, and cut. The left gastro-epiploic vessels are divided far toward the left at the site of the intended transection of the stomach on the greater curvature. The gastro-colic omentum is now separated toward the right. The pancreas is freed by blunt and sharp dissection. This step is made more difficult if there is an ulcer on the posterior wall of the duodenum. Actual penetration of the ulcer into the pancreas may necessitate opening into the ulcer in the process of separation. If such an ulcer is opened, its base should be swabbed with iodine and a tag of omentum fixed in it with sutures. In certain cases in which it is deemed impracticable to open the ulcer, the stomach may be resected proximal to the pylorus, and inverted. If the ulcer has been elevated from the pancreas, the duodenum is grasped between forceps, severed, and inverted by a Parker-Kerr suture using fine catgut reinforced with silk. The choice of the site of division of the stomach has varied with different surgeons. The Author believes that subtotal removal of the lesser curvature and spur formation by partial closure of the stomach with the vertical position of the stomach in the standing position are correct. He divides the stomach downward and toward the left for the purpose of removing more of the greater curvature than was recommended by Finsterer, but he maintains the vertical position of the stomach by suturing the opening in the mesocolon above the anastomosis. The sacrifice of a greater amount of the greater curvature makes it technically easier to anastomose the stomach and jejunum without spur formation at the greater curvature end of the anastomosis. The Author recommends anastomosis made near to the point of origin of the jejunum; he believes that the long loop anastomosis with or without the Braun anastomosis adds a substantial danger of gastro-jejunal ulcer, and should be avoided.

In conclusion he states that spur formation at the lesser curvature border of the cut end of the stomach reinforced by the attachment of the jejunum, and the avoidance of spur formation at the greater curvature of the stomach, are necessary features in the technique.

Nine figures illustrate the technique described.

N. M. Perey, Chicago.

WHIPPLE, ALLEN O., M.D., F.A.C.S.,  
AND RAIFORD, THEODORE S., M.D.

"The Type and Grade of Gastric Carcinoma in Relation to Operability and Prognosis." *S. G. and O.*, Vol. 59, No. 3, pp. 397-410, Sept., 1934.

In this article, the Authors analyze the operability and prognosis of gastric carcinoma on a basis of the types and grades of malignancy involved. The

work is based on a series of ninety-five gastric resections for stomach malignancy operated at the Presbyterian Hospital during the past twenty-four years, and a follow-up study of sixty-three cases which survived operation.

Carcinomas of the stomach are divided into three main types:

1. The vegetative or fungating type which tends to grow into the lumen of the stomach and is found most frequently in the pars media.

2. The ulcerative type, growing both into the lumen and into the wall of the stomach, may be found in all parts of the stomach but usually in the antrum.

3. The infiltrating type, infiltrating the coat of the stomach and having very little tendency to ulcerate, is usually found in the antrum and pylorus.

Carcinoma of the stomach is graded into four groups based on the degree of malignancy. In determining the grade of malignancy, the following criteria of microscopic pathology were used.

1. The degree of cell differentiation, marked deviation in the normal glandular arrangement of the cells indicating a more malignant grade.

2. Cellular activity, indicated by the variation in shape and size of the cells and their nuclei and the variation in cell types in the same tumor.

3. The invasiveness of the tumor cells, whatever their arrangement or differentiation.

4. The lack of cohesiveness in the tumor cells, whatever their arrangement. This is considered indicative of extreme malignancy in gastric cancer.

5. Metastases in lymph nodes. Absence of lymph node involvement greatly enhances the prognosis.

The vegetating type most often shows the less malignant grades 1 and 2. The infiltrating type most frequently falls in grade 4. The ulcerating type may fall in either grade 2, 3 or 4.

The incidence of carcinoma found associated with true chronic ulcers in resected stomachs is low. They found in this series of 95 cases only six instances. The carcinomata thought to have developed on an ulcer basis, were invariably of grade 4 malignancy.

The pre-operative determination of the type of tumor and grade of malignancy is difficult. The duration of symptoms in grades 1 and 2 in their series was 7 and 8 months. The grade 3 group averaged 6 months duration and the grade 4 group 4 months duration. Those patients giving a history, suggestive of a gastric ulcer lasting over several months, and failing to abate after conservative treatment, likewise are apt to fall in the grade 3 and 4 groups.

Physical examination does not help greatly in differentiating these types of tumors. The large fungating tumors were more apt to be palpable and the large ulcerating carcinomata were more easily recognized by the radiologist than the others.

The percentage of achlorhydrias was inversely proportional to the ascending grade of malignancy. The percentage of achlorhydrias was greatest in the fundating type, least in the carcinoma-on-ulcer type, and greatest with tumors located in the pars media and least in the pylorus.

In considering the X-ray interpretation of these lesions, the Authors point out the difficulties frequently encountered in making accurate diagnosis of the pre-pyloric lesion without repeated examinations.

Regional lymph gland involvement does not necessarily contra-indicate resection, but it seriously enhances the probability of a cure. In their series, 53 per cent of the resected carcinomata had extended to the lymph glands. None of this group had lived more than 29 months after operation. On the other hand, in their patients who had lived five years or more after operation, none of them had had regional metastases.

A table is shown giving the end results in this group of cases. Twenty-six cases are alive at the present time. Seven of these have been followed ten years following operation, and two additional cases five years following operation. Thirty-five cases have died from recurrences of the tumors. Thirty-two cases died following operation before leaving the hospital. Tables are shown showing the influence of grades upon the results and also the influence of metastases upon the results.

In concluding this article, the Authors feel that the division of these cases into the degrees of malignancy and into the three gross types help materially in determining the operability and the operative procedure and in estimating the prognosis.

N. W. Swinton, Boston.

CONNELL, F. G.

*Partial Gastric Fundusctomy in Treatment of Peptic Ulcer.* *S. G. and O.*, Vol. LIX, No. 5, pp. 786-788, Nov., 1934.

The Author proposes the operation of partial fundusctomy (aiming at a diminution of the acid secreting surface rather than the removal of the alkaline secreting "ulcer bearing area") as a compromise between gastroenterostomy and subtotal gastrectomy. The indications for the operation are: peptic ulcer of the duodenum; peptic ulcer of the stomach (supplemented by local resection); peptic ulcer of the jejunum after gastroenterostomy.

A double wedge-shaped section of both the anterior and posterior fundal walls with a common base at the middle third of the greater curvature is removed.

The Author feels that the results of this operation suggest a definite field of usefulness for it in suitable cases.

A table presenting 7 cases, and one figure, accompany the article.

N. M. Perey, Chicago.

## SECTION XII—"The Clinic"

### Large Epiphrenic Diverticulum of the Esophagus

(Report of a Case)

By

B. D. ROSENAK, M.D.

INDIANAPOLIS, INDIANA

THERE is no call for an exhaustive article or a comprehensive review of the literature on the subject of diverticula of the thoracic portion of the esophagus as this material has been adequately presented in recent years in the papers of Vinson, Heacock, Barrett and others. The more restricted subject of diverticula of the lower third of the esophagus, so called "epiphrenic diverticula," has been studied and reported by Granet. He found 49 cases reported in the available literature to the year 1933. Of these, only 31 were authentic cases proved by post-mortem or by roentgen examinations. Of the 31 proved cases only 17 had direct esophageal symptoms and only 3 diverticula were situated on the left side of the esophagus.

The present case is of interest because of the size and location of the diverticulum and because of the manner in which the esophageal symptoms became manifest.

#### CASE REPORT

The patient, a white man, aged 71, was first seen in February, 1935, during an attack of choking, dyspnea and vomiting which suggested an esophageal obstruction. He was treated by elevating the foot of the bed and by the administration of opium and belladonna in a suppository. He soon became quiet and rested throughout the night. On the following day he was able to visit the office where a stomach tube was inserted into the esophagus with great care until fluid began to pour out. Thereafter his symptoms were greatly relieved. Examination of the aspirated fluid showed much undigested food-residue, pus, desquamated epithelial cells and streaks of old blood.

The patient gave the following history: Seven years ago he had frequent

attacks of dizziness and weakness which were ascribed to a possible cerebral arteriosclerosis. These symptoms were entirely relieved by a period of bed rest. Six years ago, the patient suffered the loss of his wife and was very much disturbed emotionally. During the period of mourning this man began to experience a sense of pressure in the epigastrium, associated with difficulty in swallowing and with dyspnea. Thereafter he had frequent attacks of dysphagia and choking with profuse perspiration and pallor. A few months later he began to vomit shortly after his meals. He soon learned that his epigastric discomfort as well as most of his other symptoms could be relieved by self-induced vomiting, which practice he has carried out for about four years. About six months before he was first seen he began to vomit particles of blood. He also began to lose weight at that time and has lost about 25 pounds. His appetite remained good, his bowels were always regular and there were no other significant symptoms except a constant coldness and blueness of the fingers.

On physical examination the patient was found to be in fair general condition with the exception of his obvious loss of weight, some evidence of dehydration and the disturbance of the peripheral circulation as evidenced by his cold cyanotic fingers.

On roentgenoscopy (Fig. 1) the barium was seen to enter a smooth sac as large as an orange, situated to the left of the distal portion of the esophagus and apparently resting on the left leaf of the diaphragm. Its orifice was about 3 cm. in diameter and was about 4 cm. above the cardiac opening. There was only a moderate degree of dilatation of the esophagus and no evidence of delay at the cardia. These features were demonstrated on the films. It was learned that X-rays of the esophagus had been made one year after the onset of the esophageal symptoms. These older films were obtained through the

courtesy of his physician in another city and an identical picture was seen, there being very little evidence of increase in size of the diverticulum. In addition there were two small diverticula of the second portion of the duodenum and multiple diverticula of the colon.

The mechanical factors which may explain the symptoms of esophageal obstruction in this case apparently do not include cardiospasm as the principle one, although this phenomenon occurred in 6 of the cases reported by Granet. The obstruction would seem, from the X-ray study, to be due to the direct pressure of the filled diverticulum upon the short terminal portion of the esophagus which is directed to the left and downward as it enters the stomach. A moderate degree of cardiospasm may also exist, but was not seen roentgenographically.

The symptoms of these diverticula are usually less abrupt in their onset and vary according to the size and situation of the diverticulum and the presence of such complications as cardiospasm or carcinoma. A large proportion of the cases found in the literature were asymptomatic and were discovered either at post-mortem or in the course of routine roentgen examination. The onset of the symptoms in the case herein reported was sudden and bore a definite relationship to emotional and nervous shock. This strange and perplexing circumstance often is seen and, though lacking a suitable explanation, there is an undoubtable association between psychic trauma and the reaction of an individual to visceral pain sensations. This fact recently was demonstrated in two cases of large, obviously old, pene-

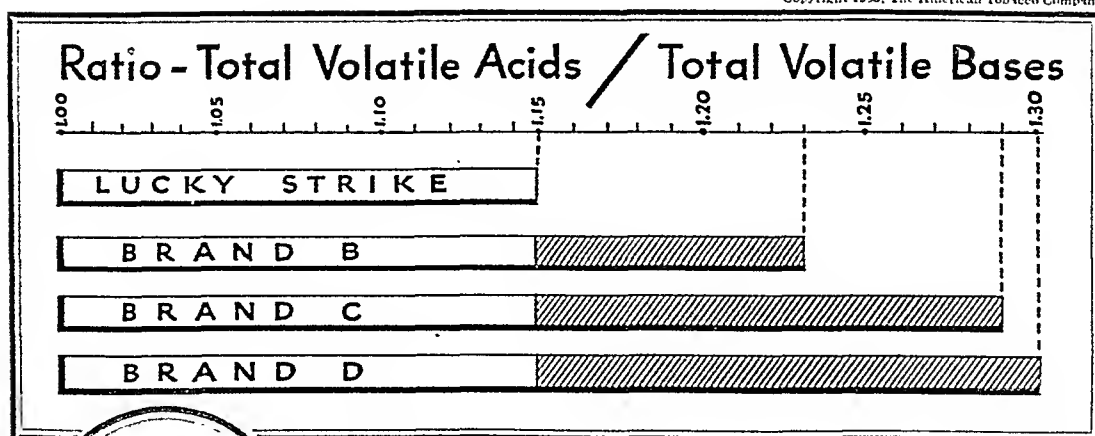
# A Quarter Century of Research Relating to A Light Smoke

Since 1911, the Research Department of The American Tobacco Company has been engaged in the solution of an extraordinarily complex problem.

The objective may be stated as: *the perfection of a cigarette with a minimum of respiratory and systemic irritants, and with a fully preserved character, i.e., a perfected acid-alkaline balance—a cigarette in which rich, full-bodied tobaccos have been successfully utilized to produce "A Light Smoke."*

A glance at the chart below—representing the excess acidity of the smoke of other leading brands of cigarettes as compared with Lucky Strike Cigarettes—demonstrates graphically how successfully this balance between acidity and basicity has been worked out in Lucky Strike Cigarettes. It shows the results of current tests, and indicates that the other popular brands have an excess of acidity over Lucky Strike Cigarettes of from 53% to 100%.

Copyright 1935, The American Tobacco Company



*a light smoke*

OF RICH, FULL-BODIED TOBACCO

trating ulcers of the lesser curvature of the stomach which were entirely without symptoms until each of the patients was subjected to a severe emotional disturbance. Something happens in these circumstances which seems to lower the individual's threshold to pain sensitivity. The situation in our patient with the diverticulum is even more astounding in that this doubtless long-standing lesion, not only began to produce pain and other subjective symptoms following a profound emotional up-

heaval, but actually began to manifest mechanical obstruction. The most apparent explanation in this case is that the psychic disturbance superimposed the element of cardio-spasm upon a moderate but asymptomatic obstruction due to the presence of the diverticulum. It is not tenable to dismiss the possibility that the sudden onset of symptoms might have been due to a coincidental esophagitis.

Diverticula in this situation probably are congenital in the vast ma-

jority of cases. The present case, in which there is an associated diverticulosis of both the duodenum and the colon is an example of multiple congenital diverticulosis. Carman states that the majority of such cases are examples of congenital diverticula. Certain mechanical factors, namely, the negative intrathoracic pressure and the increased intra-esophageal pressure during deglutition and vomiting, are adequate to explain the gradual increase in size of these lesions. Desseker has emphasized a theory which has been advanced in explanation of the etiology of pharyngo-esophageal diverticula, in a form modified to apply to the lower end of the esophagus. He points out that, in reaching the stomach, the esophagus turns to the left in its terminal portion and is oblique rather than vertical in direction. This angulation causes food to impinge on the right wall of the esophagus in this region. This view is supported by the fact that, of the 31 cases collected by Granet, 28 were on the right side. However, were this factor of definite etiologic significance the incidence of diverticula in this situation certainly would be higher. The preponderance of evidence indicates that the congenital occurrence of these diverticula is the important etiologic factor.

*Treatment* of the patient herein described, has consisted of periodic lavage of the diverticulum. The patient has gone from 10 to 14 days without recurrence of symptoms following a lavage. The obvious danger of this type of treatment must be borne in mind. No attempt is made to enter the diverticulum by use of hard, curved sounds. A very soft stomach tube is used and is passed until its eye is at the level of the orifice of the diverticulum, then water is allowed to flow in under low pressure. The end of the tube is then lowered and the fluid is allowed to return by syphonage. This procedure is repeated until the flow is clear. This mode of treatment probably is the safest that could be devised.

The great danger of this condition, in which a large area of the esophageal wall is markedly thinned and weakened, is rupture of the esophagus. The usual causes of rupture of the esophagus are instrumentation and vomiting. It has been doubted, since the time of Zenker, that a normal esophagus could be ruptured spontaneously, but there are numer-

## FRANK ANSWERS TO QUESTIONS ON BRAN

MILLIONS OF PEOPLE know of Kellogg's ALL-BRAN, so it is natural that questions are raised from time to time. To discover the scientific facts about bran, the Kellogg Company has sponsored years of research in leading nutritional laboratories. Here are some of the results of these studies, in question and answer form:

### 1. Is the "bulk" in bran irritating to the intestines?

**ANSWER:** No, not for the normal person. There are some individuals with highly sensitive intestines who should not eat "bulk" in any form—either in fruits, vegetables or in bran.

### 2. Is bran effective in relieving constipation due to insufficient "bulk"?

**ANSWER:** Laboratory tests in universities with adult people substantiate the effectiveness of Kellogg's ALL-BRAN.

### 3. Does bran continue to be effective over a period of months?

**ANSWER:** Yes. Moreover, dosage does not have to be increased, as with cathartics. In four laboratory studies on a group of healthy women, in which four tablespoonfuls of bran per person were eaten daily, the laxative effect was as satisfactory in the second month as in the first.

### 4. Is the "bulk" in bran more effective than that found in fruits and vegetables?

**ANSWER:** Yes, with many individuals. Laboratory tests indicate that, with certain people, the "bulk" in fruits and vegetables breaks down in the intestinal system. So bran is often more effective.

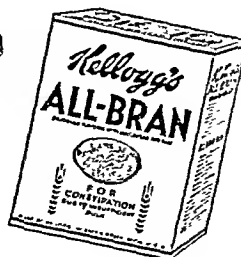
### 5. Is all bran more effective than part-bran products?

**ANSWER:** Yes. It's the actual amount of bran in the cereal that provides the "bulk" to promote regular habits. The greater amount of "bulk" in Kellogg's ALL-BRAN makes it more effective.

### 6. Does the medical profession approve the use of bran?

**ANSWER:** Kellogg's ALL-BRAN is accepted by the American Medical Association Committee on Foods.

Kellogg's ALL-BRAN provides gentle "bulk" to correct common constipation. Also vitamin B and iron. Sold by all grocers. Made by Kellogg in Battle Creek.





ous reports of cases in which a diseased or otherwise weakened esophagus has been ruptured. Most of the cases of rupture are ascribed to vomiting.

The passage of a soft rubber stomach tube and gentle lavage, in the absence of cardiospasm or other obstruction below the level of the diverticulum, certainly is attended by less increase in intra-esophageal pressure than occurs during the act of vomiting; hence there is less danger of rupture of the esophagus when this treatment is carried out properly.

Two cases are reported in the literature who were treated surgically by trans-thoracic excision of the sac. Both of these patients died. The risk of this operation seems too great to warrant its execution on individuals who can be relieved by the simple procedure described above.

#### REFERENCES

1. Vinson, Porter: Diverticula of the Thoracic Portion of the Esophagus. *Arch. Otolaryngol.*, 19-508, 1934.
2. Heacock, C. H.: Diverticula of the Thoracic Portion of the Esophagus. *South. M. J.*, 23-517, 1930.
3. Barrett, N. R.: Diverticula of the Thoracic Esophagus. *Lancet*, 1-1109, 1933.
4. Granet, Emil: Epiphrenal Diverticulum of the Esophagus. *Am. Jour. of Surg.*, 19-259, 1933.
5. Carman, R. D.: Roentgen Diagnosis of Diseases of the Alimentary Tract. Ed. 2, Saunders, 1920.
6. Desseker, C.: The Epiphrenal Pulsion Diverticula of the Esophagus. *Arch. f. Klin. Chir.*, 128-236, 1924.
7. Zenker and Ziemssen: Diseases of the Esophagus. *Cyclopedia of the Practice of Medicine—Ziemssen*, 1878.

## ABSTRACTS

LADD, WILLIAM E., M.D., AND GROSS, ROBERT E., M.D.

*Intussusception in Infancy and Childhood. Arch. Surg., Vol. 29, No. 3, pp. 365-385, Sept., 1934.*

This article is a report of 372 cases of intussusception, treated at the Children's Hospital of Boston between 1908 and 1932.

Eighty-seven per cent of these cases were under two years of age and seventy per cent were between the ages of four and eleven months. Sixty-one per cent were boys, and thirty-nine per cent were girls.

In only five per cent was there a demonstrable etiological factor, Meckel's diverticulum being the most common. Benign tumors of various kinds caused most of the others. Seventy-five per cent of the cases were invaginations of the ileum into the colon.

The important and most frequent symptoms were attacks of abdominal pain, pallor, sweating, vomiting and

bloody stools occurring in a previously healthy child. The prominent physical findings were shock, dehydration, a palpable abdominal mass (84 per cent), blood from the rectum (50 per cent). X-ray studies were characteristic when made, but the Authors do not feel that this is necessary in the average case of acute intussusception.

The treatment was by operative reduction and resection when reduction failed. In thirty resections done, only two were successful. However, the Authors point out that in the last five years, in 90 patients only two resections have been necessary. The mortal-

ity in this group has steadily dropped through the years, being 59 per cent in the 1908-1912 group, and 14 per cent in the 1928-1932 group. In the last five years, 60 cases which were operated upon during the initial thirty-six hours of the disease recovered without any mortality.

The removal of a Meckel's diverticulum or other cause of intussusception should be deferred, if possible, for a second operation. Reducing the time between the onset of symptoms and the operation was the most important single factor in reducing the mortality in this group of cases.

## The World's Most Famous Natural Alkaline Water

### PRESCRIBED BY PHYSICIANS THE WORLD OVER

VICHY CÉLESTINS, the most famous of natural alkaline mineral waters, is indicated in stomach and liver affections and digestive disorders in general; in gout, arthritis associated with uric acidemia, uricemia, and nephrolithiasis of uric acid origin. During convalescence, it eases and expedites the journey back to health. Vichy Célestins is obtainable everywhere.

BOTTLED ONLY AT THE  
SPRING IN VICHY, FRANCE



# VICHY CÉLESTINS

Write for booklet on Therapeutic Value of Vichy with Medical Bibliography.  
AMERICAN AGENCY OF FRENCH VICHY, INC., 198 Kent Ave., Brooklyn, N. Y.

Pre and postoperative care of this group of patients is discussed.

The incidence of recurrent intussusception in this group of patients was 1.8 per cent. Because of this fact, the Authors do not feel that time should be wasted at the primary operation in attempting procedures designed to prevent recurrence.

N. W. Swinton, Boston.

GAITHER, ERNEST H.

"Gastric Carcinoma: A Clinical Research. Preoperative Course and Post-Operative Results." *South. Med. Journ.*, 28:107-114, Feb., 1935.

In an analysis of 245 cases of operatively demonstrated gastric carcinomas some depressing findings are recorded but there is offered the following revision of symptomatology which may

aid in earlier diagnosis. The onset of symptoms was usually not gradual but the subsequent course may be abrupt or gradual. There was no characteristic cancer pain. The presence of pain rather than simple discomfort is suggestive enough. It may resemble ulcer pain, be constant or intermittent and while usually in the epigastrium may be any place in the abdomen. Anorexia was frequently an outstanding symptom but many will not complain of loss of appetite. Hamatemesia was rare but of coffee-ground type when it occurred. Nausea and vomiting were found more marked and prevalent than expected. 70 per cent of the patients were constipated. Tarry stools were reported in but few cases probably because of the patient's faulty judgment but the presence of occult blood was generally constantly present and of considerable diagnostic importance. Practically every patient shown an appreciable loss in weight and in the majority of cases it was enormous.

There was an almost total absence of complaints of soreness while localized tenderness was frequently found. Anemia was present in the majority of cases and often quite marked with no evident ill-effects. Family history for carcinoma was practically nil. Positive Wassermann reactions were present in 8 per cent of the cases but apparently unrelated to the carcinoma. Achylia or hypochlorhydria were usual but even hyperchlorhydria was demonstrated in some cases. Cachexia was detectable in very few cases. Even large masses were frequently not palpable. The average age was 55 and 83 per cent were male.

Only 25 post-operative patients could be gathered for study. Even those who had only a palliative operation were greatly relieved symptomatically. Unless absolutely contraindicated operation should always be undertaken. Periodic health examinations and a revaluation of symptoms should make possible earlier diagnosis which is the great need now.

J. Duffy Hancock, Louisville.

H. E. S. STEVEN.

*Diverticula of the Jejunum.*  
*Lancet*, 227, pp. 704-705, Sept. 29, 1934.

Diverticula of the jejunum are extremely rare only 60-70 cases being reported in the literature.

A farm worker, aged 40, was sent into the Cairo hospital with a diagnosis of appendicitis. The history was suggestive of chronic incomplete intestinal obstruction and it was considered advisable to investigate the case before operation. A bismuth meal was given. This precipitated a crisis and laparotomy was performed.

Volvulus of the upper part of the jejunum was found and multiple diverticula were observed extending down the jejunum and ileum. They varied in



FALL



WINTER

## CAROTENE (PRO-VITAMIN A) IS AN ALL YEAR SOURCE OF VITAMIN A ACTIVITY

for ADULTS and CHILDREN

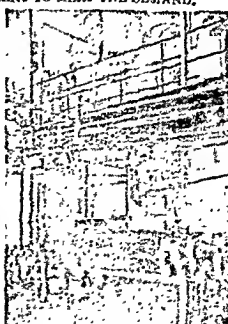
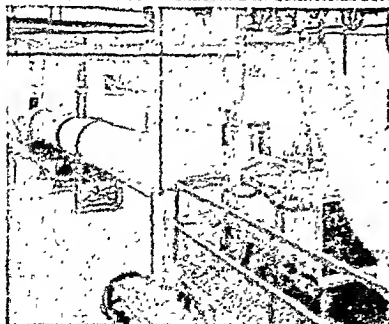
Q Many regard Carotene [Pro-Vitamin A] as a valuable aid in maintaining a healthy condition of the mucous membranes and therefore, believe that it helps to build general resistance against infections. Q Smaco Carotene-in-oil is made from plant sources exclusively. Consequently it has no fishy taste. Small, easy, drop or capsule doses. Q Also offered combined with Vitamin D concentrate.

S.M.A. Corporation

Cleveland, Ohio



GLIMPSES OF SOME OF OUR EQUIPMENT FOR PRODUCING CAROTENE IN QUANTITIES SUFFICIENT TO MEET THE DEMAND.



size from a pea to that of a tangerine orange. All had their origin from the border of the intestine near the mesenteric attachment. They contained a watery like fluid.

The abdomen was closed after relieving the volvulus and the patient made an uneventful recovery. Subsequent X-ray pictures showed gradual drainage of the diverticula.

John T. Day, Montreal.

WHIPPLE, ALLEN O., AND RAIFORD, THEODORE, S.

*The Type and Grade of Gastric Carcinoma in Relation to Operability and Prognosis. S. G. and O., Vol. LIX, No. 3, pp. 397-409, Sept., 1934.*

In attempting to explain the great variation in mortality rate and interval results in the surgical treatment of carcinoma of the stomach, the Authors mention the importance of limiting gastric resections to individual surgeons of mature experience with permanent assistants, pre-operative care and post-operative care. They believe that the interval results depend on those factors, and on the type and grade of the carcinoma. Three types of carcinoma of the stomach are recognized:

1. The vegetative or fungating type which shows a tendency to grow into the lumen of the stomach more than to infiltrate the walls.
2. Those that grow into the lumen, and into the walls showing a tendency to ulcerate.
3. Those that grow into and infiltrate the coats of the stomach with less tendency to ulcerate.

The vegetative type was found most frequently in the pars media; the ulcerating type most commonly in the antrum, while the infiltrating type was found most frequently in the antrum and pylorus.

Grading of the malignancy of tumors is at best only relative and involves a certain personal factor. The Authors recognize four grades of malignancy. The grade is determined according to the following criteria:

1. The degree of cell differentiation.
2. Cellular activity-variations in the size and shape of the cells, and their nuclei.
3. The invasiveness of the tumor cells; this is noticed by the presence in adjacent tissues.
4. The lack of cohesiveness in the tumor cells.
5. The presence or absence of metastases in the lymph nodes.

There is a fairly definite relation between two of the types and grades; the vegetative type is most often less malignant, that is, in grades 1 and 2. The infiltrating type is usually in grade 4. The ulcerating type may be grade 2, 3, or 4.

The duration of symptoms before medical aid is sought bears an interesting relation to the grade of the tumor.

In grades 1 and 2 the average duration of symptoms was seven or eight months, while for grade 3 it was six months, and for grade 4 it was four months. A case showing a palpable tumor mass with a filling defect in the pars media without great loss of weight and strength, without a severe anaemia, and with achlorhydria would be considered as a probable fungating type of grade 1 or 2. A case showing rapid loss of weight and strength, an anaemia, free hydrochloric acid, and X-ray findings showing an infiltrated wall in the region of the pylorus would

be considered as an infiltrating type of grade 3 or 4. The Authors do not consider adherence of the tumor mass to adjacent organs as a contra-indication to resection because such adherence may be inflammatory; they cite two cases in which the colon was resected, and in which the results were excellent.

In the series of cases reviewed by the Authors the percentage of deaths from recurrence rose in direct proportion to the grade of malignancy of the tumor.

In conclusion the Authors suggest that these cases be studied clinically and pathologically by a combined group

# No Leakage • No Griping

• • • • •

For the rational treatment of constipation

HALEY'S

# M-O

REG. U.S. PAT. OFF.

AN EMULSION OF MILK OF MAGNESIA AND PURE MINERAL OIL presents the lubricating, softening effect of mineral oil, with the gentle, stimulating action of milk of magnesia.

Haley's M-O is a palatable, stable emulsion, supplied in 8-oz., 16-oz. and 32-oz. bottles.

Dose: 1-2 tablespoonfuls, before breakfast and at bedtime.

SAMPLE ON REQUEST

The Chas. H. Phillips Chemical Co.

170 Varick Street

New York, N. Y.

of physician, surgeon, roentgenologist and pathologist. They suggest a modification of the plan first suggested by Scott. Their plan embodies a clinical classification in which the malignant cases are definitely segregated from the benign. Such a classification contains four groups as follows:

1. Ulcer suspect.
2. Ulcer verified.
3. Ulcer verified, carcinoma suspect.
4. Ulcer verified, carcinoma verified.

Group 1 includes a large number of cases whose histories suggest an ulcer, but in which there is no confirmatory evidence. Treatment in this group is palliative.

Group 2 contains those cases in which the clinical impression of ulcer has been confirmed by roentgenological studies. Conservative treatment is advised in these cases. Each case should be carefully followed for recurrence. It is important to follow these cases carefully for it is not uncommon for an ulcerating carcinoma to apparently improve temporarily on such treatment. If symptoms are not markedly abated, or if they become worse, the patient must pass on to group 3.

Group 3 contains the group in which ulcer is verified, carcinoma suspected. Treatment of this group varies with the individual physician or surgeon. It

is in this group that exploration should be done. When the presence of carcinoma is verified, the patient passes on into group 4.

The Authors quote the criteria of Lahey and Jordan for the limits of conservative treatment in group 3. They require that, within a period of three weeks, symptoms be completely relieved; that the lesion, by repeated X-ray studies, must show a definite decrease in size; and that blood disappear from the faeces and gastric content.

Nine figures and nine tables accompany the article.

N. M. Percy, Chicago.

JUDD, E. STARR, AND WALDRON, GEORGE W.

*The Present Status of the Surgical Treatment of Peptic Ulcer.* S. G. and O., Vol. LIX, No. 3, pp. 350-353, Sept., 1934.

The Authors state that the surgical treatment of peptic ulcer is not entirely satisfactory in certain nervous, high-strung individuals in whom the symptoms seem to parallel the degree of nervous strain, and in young persons. The best that one can accomplish for such patients is to keep the symptoms under control a part of the time. In another group of patients in whom the symptoms are atypical, and in whom the laboratory tests fail to show the presence of an ulcer, surgical treatment is unsatisfactory. Surgical treatment in such cases should be confined to a local operation, that is, the removal of the cap of the duodenum with the ulcer and the anterior two-thirds of the pyloric sphincter, making closure by a gastro-duodenostomy. This re-establishes the continuity of the gastro-intestinal tract, and eliminates all possibility of spasm due to sphincter action.

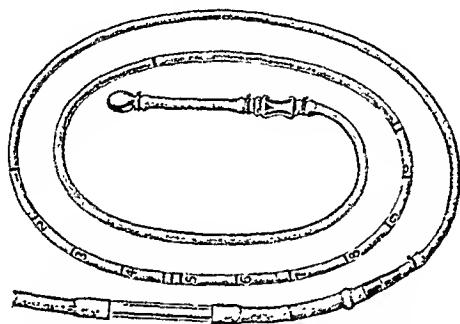
In cases in which the duodenum cannot be mobilized without undue risk, and in which a gastro-jejunostomy is not a feasible procedure, it has been found satisfactory to make a lateral anastomosis between the pyloric end of the stomach and the first portion of the duodenum, leaving the pyloric sphincter undisturbed. This operation is of greatest use in cases in which it is necessary to take down an old gastro-jejunostomy because of the development of a jejunal ulcer, and in which the lumen of the duodenum is inadequate because of scar tissue contraction.

In elderly patients with marked obstruction, and low gastric acidity, gastro-jejunostomy is still the most satisfactory procedure. Gastric resection is necessary in less than five per cent of the cases.

The Authors contend that without microscopic study it is impossible to determine whether a gastric ulcer is benign or malignant, and for that reason it should be treated surgically. V-excision of the lesion with gastro-jejunostomy was given the most satisfactory results in many cases. In some

## DR. TWISS' DUODENAL TUBE

Designed by Dr. John Russell Twiss, New York City



**A** RADICALLY new tube with bucket and terminal swivel weight that guides tube and bucket easily through pylorus into duodenum without kinking or curling.

The use of slightly larger and more resilient tubing tends to prevent looping in stomach.

The small diameter of solid terminal tip makes engagement in pylorus easier and the smaller size tubing attached is drawn after it by peristaltic action on the terminal ball. Thus the small size bucket which is attached by the means of swivel connection between terminal ball and bucket permits torsion of terminal ball without affecting duodenal tube and bucket or causing it to loop in the stomach.

Construction of slots in bucket allow free flow of fluid. Concavity prevents adherence to visceral walls. Terminal

ball and bucket are attached to rubber tubing by silk thread, but without use of knots.

The rubber tube has the standard one, two and three ring marking, but in addition the tube is calibrated in inches from the two-ring marking to a point four inches beyond the three-ring mark. This calibration is advantageous where drainage is to be repeated, because the three-ring mark represents only the distance where bile may be obtained in the average patient. Since there is a variation of length required, the correct length may be recorded for reference.

For descriptive folder giving full technical details, usages and advantages, address:

I. SKLAR MANUFACTURING CO.,



BROOKLYN, N. Y.

instances the technical procedure is simplified by taking out the pyloric part of the stomach with the ulcer.

The Authors believe that two procedures tend to correct the etiological forces more than any others; they are: (1) lateral gastro-duodenostomy, and (2) excision of the ulcer along with the cap of the duodenum and the anterior two-thirds of the pyloric sphincter, closing by gastro-duodenostomy. Those operations they believe should be employed more often.

N. M. Percy, Chicago.

BALFOUR, DONALD C.

*Indications for the Surgical Treatment of Carcinoma of the Stomach. S. G. and O., Vol. LIX, No. 3, pp. 543-560, Sept., 1934.*

The Author states that when the diagnosis of carcinoma of the stomach has been made, or when a lesion which may be malignant has been demonstrated roentgenologically, the basic indication for treatment is that unless definite metastasis can be demonstrated, surgical exploration of the growth is warranted. The conscientious surgeon should view the situation from the standpoint that cure may sometimes be brought about in cases which, preopera-

tively, appear to be too far advanced for cure.

Fortunately early distant metastases occur in the supra claviclar lymph nodes and in the peritoneum of the rectal shelf. Nodules in either site denote incurability but not always the undesirability of exploration. In rare instances biopsy will show that the supra claviclar glands are inflammatory rather than malignant. If they are malignant operation is precluded even though marked obstruction may be present. The patient who is in good general condition, but who has an antral lesion which is producing obstruction, may be greatly benefited by operation. Metastases to the liver, or to the region of the umbilicus, are contra indications to operation regardless of other circumstances. The presence of fluid in the abdomen, or of extra-gastric masses, definitely contra-indicate operation. (Smithies' "signs of inoperability"). Other things being equal, the younger the patient the more clear the indication for operation, and it is on relatively younger patients that the most extensive operations are justified. Fluoroscopic and roentgenographic examination by a competent roentgenologist will give more definite char-

acteristics of the growth than all other methods combined.

Exploration of the abdomen is carried out under local anaesthesia alone, or combined with a general anaesthetic. If peritoneal implants are found, the surgical treatment cannot be considered as curative. Occasionally the primary growth may be so situated that it is advisable to perform a resection to protect the patient from the early onset of obstruction. An apparently isolated, small metastatic nodule in the liver may not be a contra indication to resection. Widespread involvement of the regional lymph nodes is a very unfavorable prognostic sign. Involvement of the supra, and infra, pyloric nodes is of more serious prognostic value than involvement of the nodes along the greater and lesser curvatures. If the growth is found to be adherent to the pancreas, or the liver, but free from other structures, resection should be carried out as the adherence may be entirely inflammatory. Definite involvement of practically the entire lesser curvature is usually a contra indication to radical operation. The exception, however, is in those rare cases in which the entire stomach is involved; in this type of case total gastrectomy is most likely to be

## EVERYTHING FLORIDA OFFERS

At Exceptionally Attractive Rates

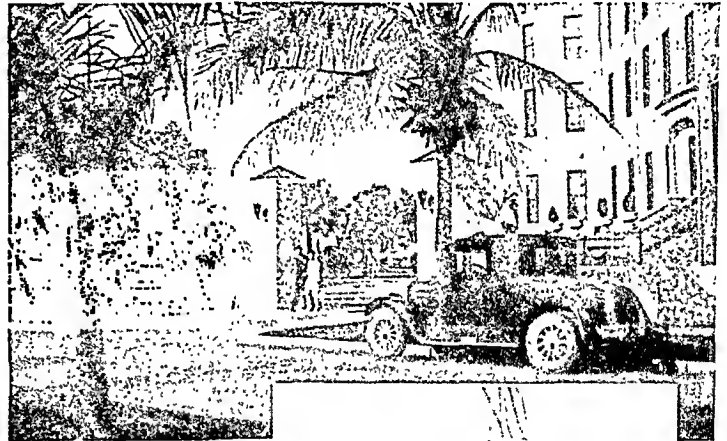
**H**OTEL Charlotte Harbor is one of Florida's finest and loveliest resort hotels. In a beautiful setting, directly on the water at Punta Gorda on the West Coast. Own facilities for bathing, golf, tennis and trap shooting—wonderful quail shooting and fishing. Unique swimming pool of mineral water for warm, healthful bathing. All Florida offers—yet rates are only

Weekly \$42 to \$56 Single and \$84 to \$112 Double Including Meals and Private Bath.

All rooms face the water and front grounds, all with private bath. Suites may be arranged. Special attention is given to the table and service for which the hotel has long been noted. On Tamiami Trail, 100 miles south of Tampa, or by railroad to Punta Gorda. Select Christian clientele.

Now open, special rate concessions up to January 1st. Wire reservations collect or send for booklet to the manager, Mr. Floyd Alford, Jr.

**HOTEL CHARLOTTE HARBOR**  
PUNTA GORDA, FLORIDA



Above: Side entrance showing part of tropical gardens. Right: Tarpon caught near Hotel.



feasible. Accurate determination of the extent of the infiltrating type of growth is difficult, while determination of the extent of the ulcerative and colloid types of growth is usually accurate by palpation. The largest tumors which may still be operable are of the colloid type.

If resection seems to be justifiable, there are many variations in the methods by which it may be accomplished. No attention need be paid to a consideration of gastric acidity. The stomach should be anastomosed to the jejunum by a suitable method. The Billroth I method of resection is inadvisable, in that recurrence of the growth will be so situated as to produce obstruction early.

So far as palliation by resection is concerned with the exception of resection, the Author believes that exclusion of the growth is the most satisfactory procedure. Gastro-enterostomy too frequently fails to accomplish what it is hoped to do as a palliative procedure.

N. M. Percy, Chicago.

GARRIS, R. W., M.D., AND MERKEL, W. C., M.D.

*The Symptom Complex of Complete External Pancreatic Fistula. S. G. and O., Vol. 59, No. 4, pp. 590-598, Oct., 1934.*

This article discusses the symptom complex of complete external pancreatic fistula, its diagnosis and treatment, and reports a typical case.

## SYMPATHETIC RELATIONS

of the gastrointestinal tract are effectively allayed while the fundamental organic trouble is properly treated, in the adjunct use of

## TAUROCOL Bile Salts Tablets



A combination of bile salts, extracts of cascara sagrada, phenolphthalein and aromatics. TAUROCOL is a cholagogue widely prescribed by physicians for more than a quarter of a century. Clinical Record Forms for the asking. Samples and information on request.

The Paul Plessner Co.

Detroit - - - Michigan  
J. D. 12-35

Various experimental and clinical studies are reviewed and it is shown that complete exclusion of pancreatic juice from the intestines is lost by external fistula, produces a highly characteristic clinical syndrome consisting of striking anorexia, nausea, intermittent vomiting, steatorrhoea, extreme exhaustion, anhydremia and emaciation, with a rapid lethal determination.

A typical case is presented. A woman aged 61 developed this typical syndrome following a cholecystectomy and died five weeks post-operatively. At autopsy a pea size adeno-carcinoma of the ampule of Vater, causing complete ob-

struction of the common and pancreatic ducts, was found.

In treating this condition a low carbohydrate, high-alkalin diet should be given. Ereptone by mouth or by enema has been used advantageously. Sheep's pancreas in amounts of over one-quarter pound daily are beneficial. The feedings of fistula bile and intestinal juice by stomach tubes improve these patients. Operative procedures are either designed to extirpate the fistulous tract, if the fistula is incomplete, or to anastomose the pancreas to the stomach or duodenum.

N. W. Swinton, Boston.

## Viable Bacteria Reduced To Zero (Or Near Zero)

In 15 series of samples of the defecate from a number of human subjects. The subjects were not injured by the medication, as determined by thorough clinical and laboratory examinations immediately after cessation of medication and for a number of months subsequent thereto.

The medications employed were two saponaceous glycerites of Alpha Naphthol designated:

## ALPHA NAPH CO AND JELLY OF ALPHA NAPH CO

The Alpha Naph Co was taken in water and orange juice. The "Jelly" was administered in enteric coated capsules opening in the intestinal tract.

A resume of the reports, and adequate supplies for clinical test, will be gladly sent to any physician interested, with our compliments.

**CAREL LABORATORIES**  
REDONDO BEACH - - - CALIFORNIA



## SECTION I—*Clinical Medicine: Diseases of Digestion*

### Psychogenic Factors in Ulcerative Colitis\*

By

ALBERT J. SULLIVAN, M.D.†

NEW HAVEN, CONNECTICUT

A CONVINCING method of demonstrating the importance of psychogenic factors in the symptomatology and therapy of chronic ulcerative colitis would be to relate the detailed histories of each of our cases. Unfortunately, the space at our disposal makes this impossible. In first calling attention to this relationship in 1930, Murray (1, 2) presented impressive case studies. In 1932 we (3) reported in detail the first six of this series of fifteen cases which have been seen at the New Haven Hospital during the past five years.

The purpose of this report is to emphasize the frequency with which psychogenic factors are etiologically associated with this disease, the surprising number of personality traits that these patients have in common which seem to be of significance and the excellent and often dramatic results obtained from psychotherapy.

In Table I are arranged the data pertaining to the colitis at the time the patients presented themselves at the hospital. These are offered as evidence to indicate that we are dealing with real organic disease and not merely functional diarrhea. No attempt will be made to give the average duration or the average febrile reaction, for averages mean little in a disease as varied in its manifestations as is ulcerative colitis. Our cases range from the acute fulminating type of one month's duration to the more usual one of six or seven years' duration with numerous remissions and recurrences. Most of the patients had been hospitalized elsewhere and therapy in each case had usually included diet, irrigations, anti-amebic therapy, blood transfusions and vaccines.

One of the most interesting facts revealed by Table I is that with the exception of three cases, the disease began between the 20th and 30th years of life. This is considered of significance by psychiatrists because it is in this decade that most individuals are called upon to assume adult responsibilities. The average individual establishes himself both financially and sexually during this decade.

Many commentators have called attention to the frequency with which vegetative nervous system imbalance is found in patients with ulcerative colitis. Unfortunately, in our cases, most of the signs and

symptoms of *autonomic imbalance* were not recorded. In Table II are given the data which were most frequently recorded. Most striking is the frequency of dilated pupils and an elevated pulse rate. In only two cases did the accelerated pulse seem to be associated with an elevated basal metabolic rate.

*Bowel habit* previous to the onset of colitis is included in Table II because of its obvious relation to the vegetative nervous system and because it may give an inkling of the mechanism responsible for this type of ulcerative colitis. In five cases there was a story of previous constipation, apparently of the spastic variety. Three gave a history of always having had a tendency to pass two or three soft or loose stools a day. Three patients told of loose or diarrheal stools whenever they were excited or emotionally upset. Case 14, for example, would have two or three diarrheal stools while waiting to go to a dance or to the theatre.

In Table III are given factors concerning the *personality* of the patient and the patient's social relationships which seem to us to be of significance.

*Occupational and Intellectual Endowment.* It seems to be of no little significance that only two of the fifteen patients were of low intelligence, three of average intelligence and that ten were of high intellectual capacity. This is especially striking when it is emphasized that thirteen of the fifteen were ward or dispensary patients.

*Sense of Neatness.* It is interesting to note that so many of these patients were inclined towards introjection. Most of the housewives in the series were of the "neat and fussy" variety. The males were prone to express themselves by their care in personal appearance and dress. One of the patients became highly disturbed if anyone disarranged her toilet articles. One can only speculate as to whether the diarrhea is a subconscious symbolic method of expressing one's resentment at a neat and clean world which has betrayed one.

*Emotional Tension.* By this we refer to an inability to throw off the effects of an emotional episode. This mental characteristic is best expressed by one patient who said, "I wish I could get over my troubles and forget things as soon as they are over as most people can. When I get into a quarrel or some other unpleasant thing comes up, I stew it over for three or four days." Ten of our patients observed this type of

\*Presented at the 38th Annual Session of the American Gastroenterological Association, Atlantic City, N. J., June 10-11, 1935.  
Approved by the Publications' Committee of the Association.  
†Associate Clinical Professor of Medicine, Department of Medicine, Yale University, School of Medicine.

prolonged emotional reaction. Strangely enough they showed few outward signs of this bottled-up emotion. They seemed to suppress the usual methods of expressing anger, despair, triumph, and were often considered to be rather nonchalant by their friends.

**Financial Worries.** Eight of the group of 15 cases gave histories of financial troubles; in one case it took

the colon in a few hours. This fortunate circumstance allows one to concentrate on the emotional adjustments just prior to the attacks. Rarely, if ever, is the fundamental problem discussed by the patient at the first or second interview. Usually several weeks of daily talks with the patient are necessary before real progress can be expected. It has been an interesting

TABLE I  
*Organic Findings*

| No. | Sex    | Age | Duration of Disease | Duration of last Attack | No. of Attacks | Maximum Temp. | No. of Stools Daily | Weight Loss | Hgb. | Proctoscopic Changes | Extent of Disease by X-ray     |
|-----|--------|-----|---------------------|-------------------------|----------------|---------------|---------------------|-------------|------|----------------------|--------------------------------|
| 1   | Female | 33  | 6 yrs.              | 12 mo.                  | 5              | 102°          | 8                   | 35          | 60%  | Typical              | Splenic Flex. to Rectum        |
| 2   | Female | 26  | 7 mo.               | 7 mo.                   | 1              | 100°          | 8                   | 10          | 50   | "                    | Sigmoid and Rectum             |
| 3   | Male   | 22  | 1 mo.               | 1 mo.                   | 1              | 101°          | 8                   | 13          | 75   | "                    | Splenic Flex. to Rectum        |
| 4   | Female | 39  | 1 yr.               | 12 mo.                  | 1              | 100°          | 8                   | 20          | 85   | "                    | Entire colon                   |
| 5   | Male   | 25  | 7 yrs.              | 7 yrs.                  | 1              | 99°           | 6                   | 10          | 85   | "                    | Entire colon                   |
| 6   | Male   | 56  | 2 mo.               | 2 mo.                   | 1              | 98°           | 15                  | 0           |      | None                 | Caecum to Mid Transverse Colon |
| 7   | Female | 23  | 6 mo.               | 2 mo.                   | 3              | 99°           | 5                   | 20          | 65   | Typical              | Mid Transverse Colon to Rectum |
| 8   | Female | 29  | 4 mo.               | 4 mo.                   | 1              | 99°           | 8                   | 10          |      |                      |                                |
| 9   | Female | 28  | 3 yrs.              | 1 mo.                   | 3              | 103°          | 10                  | 15          | 45   | Typical              | Mid Transverse Colon to Rectum |
| 10  | Male   | 43  | 3 mo.               | 3 mo.                   | 1              | 99°           | 6                   | 15          | 95   | Slight               | Sigmoid and Rectum             |
| 11  | Male   | 22  | 1 yr.               | 3 mo.                   | 3              | 98°           | 4-10                | 10          | 85   | Typical              |                                |
| 12  | Female | 23  | 1 yr.               | 12 mo.                  | 1              | 102°          | 15                  | 60          | 55   | "                    | Hepatic Flex. to Rectum        |
| 13  | Male   | 32  | 4 yrs.              | 6 mo.                   | 3              | 103°          | 15                  | 40          | 70   | "                    | Hepatic Flex. to Rectum        |
| 14  | Female | 22  | 7 mo.               | 7 mo.                   | 1              | 101°          | 15                  | 20          | 35   | "                    | Entire colon                   |
| 15  | Male   | 26  | 1 yr.               | 2 mo.                   | 3              | 101°          | 8                   | 20          | 75   | "                    | Splenic Flex. to Rectum        |

the form of embezzlement and in another of theft. In these two cases and in four others, money matters played a rather prominent role in the total problem presented.

**Marital or Sex Difficulties.** Marital incompatibility or maladjustments of sex life clearly were present in all but two cases. There were marked individual variations in the problems presented.

**Abnormal Attachments.** Five of the young men had what appeared to be abnormal emotional attachments to their mothers. In five other cases there appeared to be marked attachments to some close relative.

**Relation to Childbirth.** In two wives and one husband the onset of the diarrhea was related to pregnancy or child-birth. In two other patients there was a chronological relationship but no clear psychological connection could be made out.

All the above data usually are obtained readily from the patient and are of significance in showing us in what kind of people this disease develops. However, only rarely is the specific psychological problem which is of etiological importance obtained with ease. Usually weeks must be spent in getting the confidence of the patient, talking over his problems and investigating his emotional reactions to all the factors of his environment. This would lead one into the endless investigations of the psychoanalyst if it were not for one fact: *there is an amazingly close chronological association between emotional episodes and the onset of bloody diarrhea.* In eleven out of fifteen cases the bloody diarrhea began within 48 hours of the emotional upset. In the other four cases the coincidence was not quite so dramatic in the original attack because the emotional episode was a prolonged one. However, in following the latter group it was clearly shown that exacerbations of the diarrhea were as closely dependent on the emotional state as in the first group; in fact the emotional disturbance would be reflected in

observation that the patient may show an exacerbation of symptoms during the period of several days when the fundamental problem is finally discussed. The diarrhea increases, the temperature may rise several degrees and vomiting may enter the clinical picture.

As an illustration of the difficulty in obtaining a proper history of emotional conflicts let me cite Case 13 of this series. The patient was seen in the Dispensary during some of his earlier attacks in 1931, 1932, and 1933. No psychogenic factors were discovered. In the Fall of 1934 he was admitted on the wards. Questioning by the medical students, internes, residents and myself for three weeks revealed nothing ex-

TABLE II  
*Factors Which May Bear on Vegetative Nervous System*

| No. | Pupils  | Aver. Pulse When Afebrile | Basal Met. Rate | Previous Bowel Habit           |
|-----|---------|---------------------------|-----------------|--------------------------------|
| 1   |         | 100                       | -4              | Constipated                    |
| 2   | Dilated | 95                        |                 | Loose                          |
| 3   | Dilated | 90                        |                 | Loose                          |
| 4   | Dilated | 90                        |                 | Constipated                    |
| 5   |         | 85                        | +4              | Loose                          |
| 6   |         | 75                        |                 | Emotional Diarrhea             |
| 7   | Dilated | 100                       | +35             | Constipated                    |
| 8   | Dilated | 90                        |                 | Constipated                    |
| 9   | Dilated | 110                       |                 | Constipated                    |
| 10  | Dilated | 80                        |                 | Constipated Loose when excited |
| 11  | Dilated | 80                        |                 |                                |
| 12  | Dilated | 130                       | +22             |                                |
| 13  | Dilated | 110                       | +6              |                                |
| 14  | Dilated | 120                       | -11             | Emotional Diarrhea             |
| 15  | Dilated | 90                        |                 |                                |

cept that the patient considered himself a little nervous. During this period the colitis had not improved, but on the contrary was getting worse. A psychiatrist, Dr. W. T. Brown, was called in. At the end of a week

the patient had unfolded an amazing series of episodes including gun play, forgery, a frame-up for theft, and repeated marital infidelities. These various episodes were directly associated with attacks of his colitis. Psychotherapy consisted chiefly of this unburdening and confession. Within two weeks the patient was discharged, having two or three soft-formed stools a day. In the next six weeks he gained 35 pounds and he has remained well. This case is not unusual; in fact the unfolding of the emotional background was accomplished more easily than in many of our cases.

### INCIDENCE OF PSYCHOGENIC FACTORS

During the five year period in which these 15 cases were seen, there were 10 other cases of ulcerative colitis seen in the New Haven Hospital. This would give an incidence of 60 per cent of psychogenic ulcerative colitis. Amazing as this figure may seem, it is probably too low. Seven of these 10 cases were not investigated as to possible emotional factors, as most of these were on the surgical wards. One case had four carcinomata of the colon which had developed 14 years after the onset of his colitis. There were some suggestive emotional disturbances in the background but these were not exhaustively studied. One case was a child of seven, in which psychiatric studies were extremely difficult but which is now being investigated by a children's psychiatrist. The other was a grave case complicated by severe pellagra. The patient suffered constantly from delusions, hallucinations and paranoid ideas and was labelled a schizophrenic. Because of the lack of an adequate history and because of the fact that the psychosis might have been due to the pellagrinous deficiency we could not assume that the mental state was a causative factor in the colitis. It is our opinion that about 75 per cent of cases of chronic ulcerative colitis are of psychogenic origin.

### PSYCHOTHERAPY AND ITS RESULTS

Most of these people were hospitalized three or four weeks before psychotherapy was begun. Frequently that amount of time was necessary for the discussion of the patient's problems before the real emotional disturbances were revealed. During this period, the usual extensive laboratory procedures necessary to rule out other causes of colonic ulceration were carried out. All the patients received a low residue diet with additional vitamins. All received some symptomatic therapy such as bismuth, kaolin and belladonna. Occasionally opium was necessary. A few received irrigations or oxygen by rectum. None of these therapeutic procedures seemed to give more than slight symptomatic relief. The disease usually was unchanged or even aggravated until the patient decided to talk over the fundamental psychological maladjustment.

In Charts I and II the course of the disease in these fifteen patients is graphically shown. No attempt is made to chart the attacks previous to the one which brought the patient to us. Data on the duration of the disease and the number of attacks at the time the patient entered the hospital are given in Table I. The vertical arrows indicate the point at which psychiatric investigation was begun. In most cases this coincided with the institution of psychotherapy—for the two go hand in hand. In other cases, although the emotional factors were obvious to us, the patient refused to accept or discuss them and hence there was no psycho-

therapy. The solid black areas indicate severe symptoms; the alternate black and white areas indicate periods in which the patient was having slight to moderate symptoms and the clear areas indicate complete freedom from symptoms with not more than two or three stools without blood a day.

*Brief Case Histories and Follow-up. (See Foot note)\**

*Case VII.* This case we consider of great interest. The patient's first attack of bloody diarrhea occurred when she decided to be married, her second when she had been married, and her third when she began to reside with her in-laws. She was under our care for three weeks only, in December, 1931. During this short period she refused to admit other than a chronological relationship between these events and her diarrhea. The patient thus serves as a sort of control, a case of ulcerative colitis of psychogenic origin who received no psychotherapy. A few months ago we attempted to find out what had become of her. Her course has been typical of a patient with severe colitis. There have been at least six hospital admissions in three different Massachusetts hospitals. She has been almost hopelessly ill on several occasions. She has developed some unusual skin lesions which have been reported by Dr. Brooks of Worcester (4). Her problem has never been considered from the psychogenic standpoint and she has received no psychotherapy.

*Case VIII.* This was a rather mild form of colitis of four months' duration which did not require hospitalization. The diarrhea began on her honeymoon. There were no deep psychological maladjustments, merely a few surface difficulties of a 29 year old woman, who had previously earned her own living, in adjusting to the physical and social responsibilities of marriage. Improvement was rapid and the patient has lived a normal life and has had a child. There has been no recurrence.

*Case IX.* This patient was left an orphan at 2. Her foster-father died when the patient was 12, and her foster-mother committed suicide on his coffin. There is a long history of vague fears and "the fear of being afraid" and a history of nervous indigestion. Attacks of colitis were definitely linked up with a fear of pregnancy and worry over failure of contraception devices. No deep psychological study was made. Talking over her worries seemed to banish them. Response was rapid and there was no diarrhea for nearly a year. In February, 1935, there was a short bout of diarrhea which affected all the members of the family. The patient responded to treatment in two days, the family in ten days.

*Case X.* This was a school teacher with a psychopathic personality who was subject to terrifying dreams and who was greatly worried about salary cuts. Frank discussion resulted in prompt cure of the diarrhea. He writes, "If I am subjected to an unusual excitement I have a return of diarrhea that lasts for from 24 to 48 hours."

*Case XI.* This patient, a law student, was first seen at the beginning of his third attack. These attacks and two subsequent ones began in the week preceding examinations. It was first thought that frank discussion of the rôle played by his worry over examinations would be enough to clear up his difficulties. His examinations in May, 1934, brought on another acute attack, however. Psychiatric studies by Dr. Fry revealed that the reaction to examinations was merely the apex of a broad pyramid of emotional conflicts. The patient had been placed on a pedestal by his family and much was expected of him. His diarrhea may be a method of making restitution or it may be only an excuse to justify his inability to live up to his

\*Case 1 to 6 were reported in detail in the *Yale Journal of Biology and Medicine*, Vol. 4, No. 6, July, 1932. The later cases will be reported in more detail, particularly from the psychiatric standpoint at some future date. It is suggested that the interested reader consult the *Yale Journal of Biology and Medicine*, so that he may observe the complete stories of this type of patient. Results on cases 1 to 6 from 1932 to 1935 are indicated on Chart 1.

family's expectations. Dr. Fry feels that the patient resented the emotional hold that his family had upon him and desired to break free. Good work in law school meant a good job, which in turn meant freedom. He does not believe that the diarrhea is a form of "restitution." Many of the psychological reactions in this case are suggestive of those discussed in the studies of Franz Alexander (5).

a transfusion. The failure of an expected visitor to arrive would greatly upset her for two days and her colitis would be aggravated. She fought attempts to get a complete psychiatric history. Questions on sex would result in cramps and a call for a bed-pan. It became evident that the psychiatric problem was going to be a very intricate one, probably with a homosexual component. It was de-

TABLE III  
*Personality and Social Relationships*

| No. | Occupation                      | Intellectual Capacity | Sense of Neatness | Emotional Tension | Financial Difficulties | Sex and Marital Difficulties | Abnormal Attachment to Relative | Relation of Diarrhea to Birth of Child | Immediate Attack After Emotional Episode | Outstanding Psychic Problems                                   |
|-----|---------------------------------|-----------------------|-------------------|-------------------|------------------------|------------------------------|---------------------------------|----------------------------------------|------------------------------------------|----------------------------------------------------------------|
| 1   | Housewife<br>College grad.      | High                  | Marked            | Marked            | 0                      | +                            | Brother                         |                                        | Yes                                      | Fear of pregnancy<br>Infantile sex ideas<br>Marital Continence |
| 2   | Housewife<br>Psychology Student | High                  | Marked            | Marked            | +                      | +                            |                                 | Definite                               | Yes                                      | Husband's Illness<br>Finances<br>Fear of pregnancy             |
| 3   | Clerk<br>Christian Scientist    | High                  | High              | Marked            | +                      | +                            | Mother                          |                                        | Yes                                      | Sex Difficulties<br>Theft<br>Finances                          |
| 4   | Housewife<br>Musician           | High                  | Marked            | Average           | 0                      | 0                            | ? Mother                        |                                        |                                          | Music<br>Mother's Death                                        |
| 5   | Divinity Student                | High                  | Low               | Average           | +                      | +                            | Mother                          |                                        | Yes                                      | Finances<br>Scholastic Failures<br>Sex                         |
| 6   | Unemployed                      | Low                   | Low               | Average           | +                      | +                            | Children                        |                                        | Yes                                      | Marital Difficulties                                           |
| 7   | Recent Bride                    | Average               | Average           | Marked            | 0                      | +                            | Both Parents                    |                                        | Yes                                      | 1st attack—engaged<br>2nd when married<br>3rd—in-laws          |
| 8   | Recent Bride                    | High                  | Marked            | Average           | 0                      | +                            |                                 |                                        | Yes                                      | Started on honeymoon                                           |
| 9   | Housewife                       | Average               | Marked            | Marked            | 0                      | +                            | Orphan                          | Definite                               |                                          | Vague fears<br>Fear of pregnancy                               |
| 10  | Electrical Eng.<br>Teacher      | High                  |                   | Marked            | +                      |                              | Child                           |                                        | Yes                                      | Terrifying dreams<br>Finances                                  |
| 11  | Law Student                     | High                  | High              | Marked            | +                      | ±                            | Mother                          |                                        | Yes                                      | Worry over exams.<br>Family Situation                          |
| 12  | Housewife                       | Low                   | Low               | Marked            | +                      | +                            |                                 | ?                                      | Yes                                      | Delusion of menst.<br>Marital Difficulties                     |
| 13  | Clerk                           | Average               | High              | Marked            | +                      | +                            |                                 | ?                                      |                                          | Stealing Episode<br>Shooting Episode<br>Finances               |
| 14  | Nurse                           | High                  | Marked            | Marked            | 0                      | ?                            | Mother                          |                                        |                                          | ? Homosexuality                                                |
| 15  | Civil Eng.                      | High                  | Average           | Average           | 0                      | +                            | Mother                          | Definite                               | Yes                                      | Conflict between mother and wife                               |

In January, 1935, several days before midyear examinations the diarrhea again returned. For two days he had as many as fifteen stools a day with considerable blood. Frequent interviews and much reassurance checked all the symptoms by the day of the first examination. A week after examination, while at home, he again became upset over the family situation and the diarrhea returned.

**Case XII.** A very severe colitis who was on our wards for nearly eleven weeks before the psychogenic factors could be elicited. After many of us had failed, Mr. Yoehelson, a medical student, gained her confidence. To him she admitted a self-induced abortion which she previously had kept a secret even from her husband. She had the fixed idea that she had poked a catheter from the vagina into the rectum and would menstruate per rectum for the rest of her life. There were many disturbing factors in the marital situation but after four months of careful psychotherapy by her family physician, she became symptom-free in February, 1935.

**Case XIII.** This is the patient previously referred to who had been seen in the Dispensary in 1931, 1932, and 1933, and who, after weeks of careful questioning in the hospital in 1934, finally admitted attacks of diarrhea coinciding with episodes involving gun play, forgery, and theft. Within two weeks he was nearly cured. He has gained 35 pounds and has from one to three stools daily, except on one occasion when he had an argument with his brother-in-law. For two weeks thereafter he had five stools a day.

**Case XIV.** For seven weeks attempts were made to get to the bottom of this patient's mental disturbances. There were many convincing evidences of the effects of emotion on her colon. She would have three or four stools during

aided to transfer the patient to the psychiatric ward where she could be isolated and more carefully studied. The patient refused this and left the hospital against advice. Two weeks later she was subjected to an ileostomy at another hospital and died.

**Case XV.** This patient's chief difficulty is his strong attachment to his mother and the difficulties this brought into his marital life. The patient's father committed suicide a few days before the patient was to be married. His first attack of diarrhea came during his wife's first

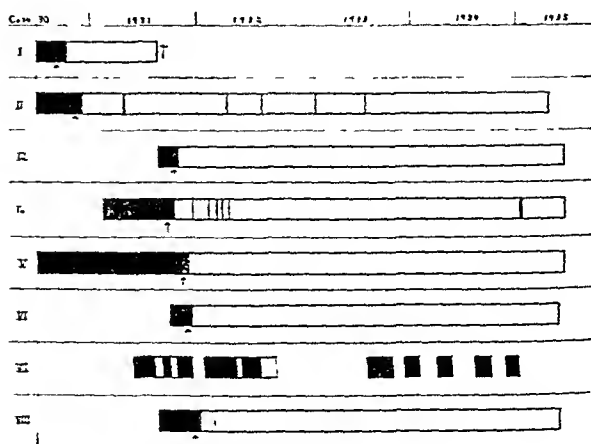


Chart 1

pregnancy when tension first developed between wife and mother. The second attack came the day his wife returned from the maternity hospital. In October his mother left on what was to be an extended visit. The patient insisted that she return. On November 15 he received a letter that she would return and on that day his most severe attack began. Most of the history was obtained from the wife

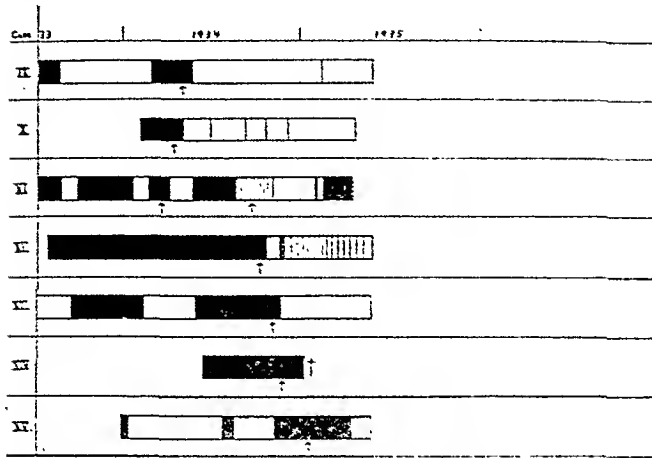


Chart 2

and mother who both agreed with our interpretation. The patient resisted and for ten days his condition grew much worse. He then swung around and admitted that the mother-wife situation was directly the cause of his diarrhea and stated that he wished he were not married. Psychotherapy which is being carried out by Dr. Brown, will probably be a long and difficult job. The diarrhea persists and probably will until he accepts or dissolves his marital status.

### DISCUSSION

In the fifteen cases presented we believe that psychogenic factors are prominent in the etiology of the ulcerative colitis. It is our opinion that psychogenic disturbances are frequently the main causative factor in the disease. We believe as a result of the follow-up study of these cases over a period of one to four years that psychotherapy is of utmost importance in the treatment of chronic ulcerative colitis.

The mechanism by which emotional disturbances can produce ulcerative colitis and by which the ulcers can be made to disappear by psychotherapy is, in the light of present knowledge, a matter of speculation. Our own working hypothesis is that the disease is closely related to "neurogenic diarrhea," a syndrome frequently seen by the gastro-enterologist. Emotion, through the vegetative centers in the diencephalon, whips the liquid contents of the small intestine down into the colon. In these particular individuals the enzymes in this liquid intestinal content may be of a higher digestive power than the normal or the natural protective powers of the mucosa of the colon may be lowered. At any rate, surface digestion of the mucosa of the colon occurs, bacterial invasion is made easy, and acute ulceration results. Because the emotional difficulty remains a chronic one, either because the situation cannot be solved or the patient is unable to face his problem, the hypermotility of the intestinal content persists and the constant irritation results in a chronic colitis. The natural reparative processes of the colon at times get the upper hand but often fresh emotional disturbances arise and we have a series of

remissions and exacerbations in the organic disease. Psychotherapy attacks the disease at its source, the nervous diarrhea. When the emotional conflict is solved, the intestinal motility returns to normal, the chief irritative factor is removed from the colon which can now take care of its bacterial invaders and the disease may promptly disappear. We offer this only as a possible explanation of the mechanism of the dramatic results obtained by psychotherapy in a few of our cases.

### CONCLUSIONS

1. During the past five years the psychiatric background in eighteen out of twenty-five consecutive cases of ulcerative colitis has been investigated. Three of these cases had some psychological difficulties which were not completely studied. In fifteen cases the emotional disturbances appeared to be of definite etiological significance.

2. In many cases the specific psychological episodes were related by the patient only after long and persistent questioning.

3. Psychotherapy in most of these cases produced striking results when many other forms of therapy had failed.

4. Brief case histories and follow-up studies on these fifteen cases are given.

### REFERENCES

1. Murray, C. D.: Psychogenic Factors in the Etiology of Ulcerative Colitis and Bloody Diarrhea. *Am. Jour. Med. Sci.*, Vol. CLXXX, No. 2, p. 239, Aug., 1930.
2. Murray, C. D.: A Brief Psychological Analysis of a Patient with Ulcerative Colitis. *Jour. of Nerv. and Men. Dis.*, Vol. 72, No. 6, p. 617, Dec., 1930.
3. Sullivan, A. J., and Chandler, C. A.: Ulcerative Colitis of Psychogenic Origin: A Report of Six Cases. *Yale Jour. of Biol. and Med.*, Vol. 4, No. 6, p. 779, July, 1932.
4. Brooke, P. A.: Erythema Nodosum—Like Lesions in Chronic Ulcerative Colitis. *New Eng. Jour. of Med.*, Vol. 209, No. 5, p. 233, Aug. 3, 1933.
5. Alexander, Franz: The Influence of Psychologic Factors Upon Gastro-Intestinal Disturbances: A Symposium. *The Psychoanalytic Quarterly*, Vol. III, p. 501, 1934.

### DISCUSSION:

DR. GEORGE EATON DANIELS (New York, N. Y.): For the last five years I have been doing considerable clinical psychiatry on the wards of the Presbyterian Hospital in New York City. About the time I started this work, Dr. Murray published his work on ulcerative colitis, so that I became interested in the problem at that time. This interest became increased through seeing patients of this type on the ward. These cases I have followed for about the same length of time as Dr. Sullivan has followed his, so in a sense they make a parallel series.

I have twelve cases of ulcerative colitis that seem to be pretty definitely on a psychogenic basis, or in which psychogenic factors are extremely important.

Now, my series of cases, I discovered in reading Dr. Sullivan's paper, had a great many similarities. One very striking thing which Murray and Sullivan have emphasized is an abnormal attachment to a relative, usually the mother. In four cases of my series the death of this relative seemed to be of great importance in the onset of the disease. One of these patients saw her mother return to her frequently in her dreams. Another made the statement that all her luck left her when her mother died.

In another case an attack of colitis appeared with the serious illness of the patient's brother, who subsequently died, and during a later attack she had very severe exacerbations of symptoms when the anniversary of this death was approached.

Another girl had an attack of ulcerative colitis whenever she was about to make the step of leaving her older sister

and her sister's son, who had made very considerable demands on her financially and in other ways.

Engagement, marriage, and child-bearing were of significance. Sexual difficulties were found in practically all the cases which is what one would expect with the type of emotional immaturity which these patients show.

I should like to add one factor which I think is of considerable importance and that is that these patients, to a large extent, are of the rather egotistic or narcissistic type. For that reason they would withstand very poorly emotional deprivations, such as the loss of someone close to them, and have very little tolerance for giving of themselves as required by marriage or the rearing of children.

In several cases the frustration of personal, professional or social ambition seemed to be an important factor in bringing on the disease.

DR. CHESTER M. JONES (Boston, Mass.): Dr. Sullivan's paper seems a most timely one, and while I am not so sure as he that psychic trauma may be the direct etiological agent in so large a percentage of cases of non-specific ulcerative colitis, I am absolutely sure that his point of view is a very fundamental one.

There is not the slightest doubt that not infrequently emotional disturbances act rapidly as an immediate cause of acute exacerbations of the disease. There is also not the slightest doubt in my mind that mental and physical rest alone is sufficient to quiet rapidly many cases of moderately severe ulcerative colitis. Hospitalization, confidence in a given physician with an enthusiastic personality, and the use of various new therapeutic procedures, frequently are considered only from the point of view of specific or nearly specific therapy, and little or no attention is paid to the fact that such measures are often effective largely because of their psychological effect on the patient.

In going over 100 cases that Dr. Urmey and I have been following for several years at the Massachusetts General, we have tried to evaluate the various factors that entered into the causation and continuance of the disease. In easily two-thirds of the cases psychogenic disturbances were obviously responsible for bringing on exacerbations, and in the whole group we felt that acute upper respiratory infections, emotional or nervous upheavals, and possibly pregnancy, were the most obvious elements entering into the onset of the disease. That there is infection of the colon is obvious, but that it represents a specific disease due to a single organism is still, I believe, far from obvious. At any rate, the conception that Dr. Sullivan has presented should be very seriously considered.

In our cases at the Massachusetts General Hospital particularly those on the private wards, psychotherapy of a

moderate or intensive type has helped exceedingly in individual instances.

DR. JOHN L. KANTOR (New York, N. Y.): Before going on to this topic proper, I should like to state that this disease is not the same as an "unstable colon," although, of course, people with unstable colons may develop chronic ulcerative colitis (idiopathic colitis, *colitis gravis*).

I think one ought to distinguish between what chronic disease does to people emotionally, and what one can claim for psychogenic factors as being the etiologic agents in a chronic disease.

As long as Dr. Sullivan and his associates are willing to emphasize the fact that *exacerbations* may be caused by emotional upsets, we are all willing to go along with them, as Dr. Chester Jones did, but if they step over the ground and say that the *initiation* of this obscure disease is of emotional origin, then I would differ.

Let me point out that any chronic recurrent, nagging, upsetting, and demoralizing disease will produce an individual with plenty of material to keep a psychoanalyst busy for days and even weeks. On the other hand, any of us, if sufficiently investigated might show psychic findings similar to those described in the ulcerative colitis cases.

Dr. Chace was good enough to tell me of a case of severe colitis in a woman who had great emotional upsets from marital difficulties and who was treated along psychic lines for months and months. Ultimately, she was found to have amebic dysentery.

As long as our friends, the psychoanalysts, will study what the disease does to people emotionally, they will probably give us information of value and may thus help us prevent recurrences, but I seriously doubt whether they are on the right track to find the original etiologic factor.

DR. ALBERT J. SULLIVAN (closing the discussion): Dr. Kantor has brought up the problem that has worried a good many of my friends when I have talked with them about this disease, and the effects of emotion on the disease. Some psychiatrist once said a psychopathic personality is any personality that has been thoroughly studied, and that may be true.

I didn't have time to bring out (I wish I could have gone over these cases individually) what I feel is the most striking thing, and that is that in twenty-four or forty-eight hours before the first attack of ulcerative colitis comes on, there is some very striking and emotional insult. That is just as true, and perhaps more true, of the first attack than of later attacks.

In these cases, if they are of psychogenic origin, there is a striking emotional problem coming just before the diarrhea begins.

## Gastroscopy with a Flexible Gastroscope\*

By

RUDOLF SCHINDLER, M.D.†  
CHICAGO, ILLINOIS

IT is well known that while gastroscopy has been carried out in an ever-increasing number of cases from 1922 on, the method has not been accepted as a routine procedure in hospitals and clinics or by the gastroenterologists themselves. This has been due,

primarily, to the difficulties and the dangers which attended the use of the rigid instrument. In 1932, however, the invention of the flexible gastroscope effected a sudden change whereby the method became at once safe and simple.

Many investigators have used it with success and have published reports. On March 29th, 1934, Benedict in this country reported a series of cases exam-

\*Presented at the 38th Annual Session of the American Gastroenterological Association, Atlantic City, N. J., June 10-11, 1933.  
Approved by the Publications Committee of the Association.  
†Visiting Professor of Medicine, University of Chicago.



ined with the flexible gastroscope. A few months later Chevalier Jackson, in a paper on gastroscopy, described his experience with this instrument.

Mikulicz first knew, in 1881, that diagnostic gastroscopy could not be made merely with open tubes, but that it had to follow the laws which govern the examination of large cavities in the interior of the body. He saw that gastroscopes would have to be built after the model of cystoscopes, and that the tip of the instrument would have to be equipped with an electric lamp which would radiate its light onto the mucous membrane of the stomach. The reflected rays could be collected by the objective of an optical system, turned by a prism to an angle of  $90^\circ$  and led to the ocular, through which the examiner was looking. Because of the length of the esophagus, the optical problems of such a system were much more difficult than in cystoscopy. A certain perfection of the optical system was reached by the instruments of Loening-Stieda and Elsner (1911). Chevalier Jackson (1907), however, tried to retain the principle of the open esophagoscopical tube. It was easy to show that this was the only possible way for the extraction of foreign bodies through the esophagus. This necessity arises, however, extremely rarely in the practice of the gastroenterologist. The greater need is that of a method which will enable him to diagnose even the smallest lesions of the mucous membrane of the stomach. The open tube is unsatisfactory for this purpose because it is too dangerous and because it does not permit adequate visualization of the interior of the stomach. The difficulties encountered were such that the development of the method was given up in 1911. When I began my work in 1921 there was no longer anyone in the world who used gastroscopy as a diagnostic method.

I used straight, rigid tubes at first. Fig. 1 shows the standard instrument which has been used since

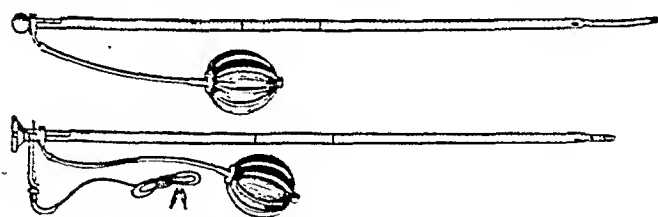


Fig. 1. Rigid gastroscopes. Schindler of 1922. A—Outer tube with air channel and obturator. B—Outer tube with optical tube.

then by many workers. A. is the outer tube with the obturator bearing a rubber finger; B. shows the outer tube after the removal of the obturator and the introduction of the optical tube. With the air balloon, the stomach could be inflated with air. The drawing shows the small holes of the outer tube through which the air passes into the stomach, the mucous membrane of which had to be at least 1 cm. from the objective in order to be seen through the optical system. The astonishing results obtained with this instrument were published in 1923 in a text book and atlas of gastroscopy, based on 400 examinations.

It was nevertheless rather soon apparent that this instrument never could be routinely used. There were two decisive objections. First, the introduction of a rigid tube was never without danger. It was found, in fact, that the introduction of open tubes was even

more dangerous than that of closed tubes with rubber obturators. Rupture of the esophagus was possible. The second objection was that, in 10% of all cases, it was not possible to pass through the diaphragmatic portion of the esophagus. A further difficulty was the fact that, in 40% to 50% of all cases, it was not possible to introduce the instrument into the lower depths of the stomach, and hence three very important portions of the stomach, the "angle," antrum and pylorus could not be observed.

It was evident that in order to overcome these difficulties it was necessary to build an instrument, the lower part of which, from about 3 cm. above the cardia up to the distal end of the tube, remained flexible during the examination. This instrument had to be capable of being bent in several planes with an angle of at least  $30^\circ$ . This seemed to be impossible. Nevertheless, in cooperation with Wolf of Berlin, we succeeded finally in the construction of such a tube.

Fig. 2 shows this instrument. Its distal end can be bent. The picture seen through the objective is quite sharp and

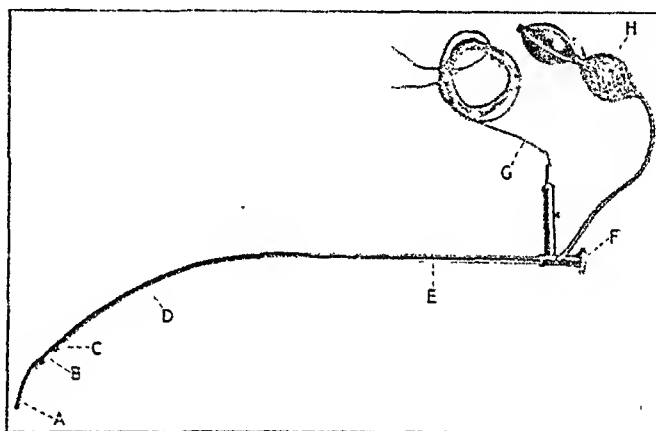


Fig. 2. Flexible gastroscopy. Schindler-Wolf, 1932. A—Rubber Finger; B—Lamp; C—Objective; D—Flexible part; E—Rigid part; F—Ocular; G—Electric cable; H—Air balloon.

clear unless the tube is bent to an angle of  $34^\circ$  or more. The rubber finger (A) leads the instrument.\* The lamp (B) and the objective (C) are constructed in the usual manner. (D) is the flexible part, which is covered by two thin rubber tubes, between which air can be injected into the stomach. In the newest model the rigid part (E) has a diameter of only 8.5 mm. (F) is the ocular. The optical system (Fig. 3) contains twenty-six lenses and is naturally extremely complicated. For this reason the instrument must be handled very carefully. Danger in this method does not concern the patient, but only the instrument.

The experience of an extended private practice has shown me that gastroscopy can become without any difficulty a routine method of the gastroenterologist, that it can be carried out in the office, that it is without real discomfort to the patient when a good local anesthesia is given, and that the patient may go immediately after it to his work. It is, however, difficult and must be learned conscientiously.

The few *contraindications* must be considered carefully. The most important ones are: Aneurysm and obstruction of the esophagus, especially of the cardia, and varices of the esophagus. When an Ewald stomach

\*A rubber sponge as used by Henning is unnecessary and not safe.

tube can be passed without difficulty, then the gastroscope can also be introduced safely.

My own experience has been derived from something over two thousand gastroscolical examinations. Approximately seven hundred of these were performed with the flexible instrument, three hundred and fifty

*sphincter antri*" (Fig. 6). The waves of peristalsis begin in the antrum beyond this point. The *musculus sphincter antri* has nothing to do with this peristalsis.

Hemorrhages and pigment spots are often seen in an apparently normal mucous membrane, but I believe they should be considered as pathological. They are

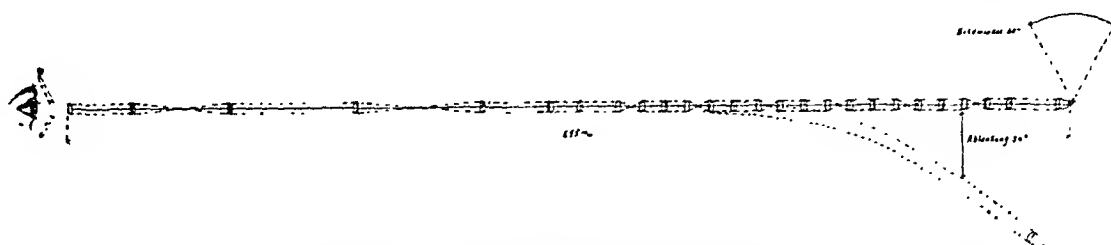


Fig. 3. Scheme of the optical system of the flexible gastroscope. (In the newest model the angle of the visual field has 85° instead of 60°).

in Munich and as many in Chicago. In many instances there were several observations in the same patient. The greatest number of gastroscopies carried out in one patient in Munich was sixty-five, in Chicago, ten.

The fundament of all of our findings has been knowledge of the normal stomach, which was studied carefully and repeatedly in many healthy persons of various ages. We found that the normal gastric mucous membrane is always uniformly orange red in color, glistening and bright. The folds of the mucosa apparently do not correspond with the well known rugous folds of the X-ray relief technic, because they are generally not parallel, but crossing and net-like. In Fig. 4 there is shown a photograph of the folds made through the rigid gastroscope. The *incisura angularis* appears as a fold. Beyond it, in at least 80% of all cases, the pylorus is seen (Fig. 5). Its activity is interesting. In the Figure, made after a colored picture, it is open. Often a small piece of the antrum remains hidden from view. In the region of the angle

frequently seen together with an ulcer or before the beginning of an ulcer, after the healing of an ulcer, or together with small hemorrhagic erosions (Fig. 7). In chronic gastritis, on the other hand, the hemorrhages seem never to change into pigment spots. These smaller changes cannot be shown by photography because the most sensitive films do not render the differences between yellow, orange red and red. This fact shows the limits of photography in endoscopy. For several years I hoped that gastrophotography would prove to be a method of value. During that time, I made endless attempts both with the "gastrophotor" and with a photographic attachment for the objective of the gastroscope, as recommended by Henning, but all to no avail. At the present time, gastrophotography has, in my opinion, no diagnostic value at all.

Ulcer of the pyloric region or of the duodenum cannot be seen with the gastroscope. Here the X-ray examination is much superior. Gastric ulcer, however, is usually well seen (Figs. 8 and 9). We have



Fig. 4. Photograph through the rigid gastroscope, showing the anterior wall of a healthy adult.

a very characteristic formation is observed, a high fold which runs over the anterior wall, the greater curvature and the posterior wall. It is cord-like and separates the cavity of the antrum from the cavity of the body. I think it is the same fold which has been described by Cole, and we may call this the "*musculus*

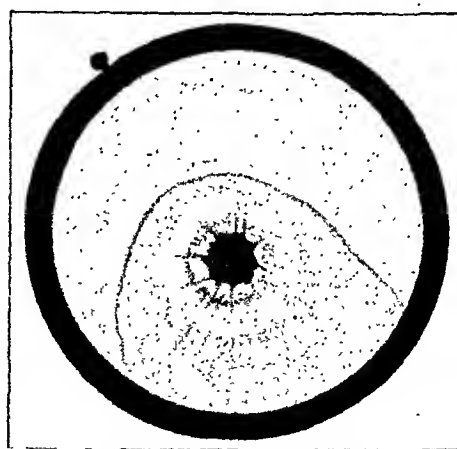


Fig. 5. Normal pylorus. In the upper part of the picture the lesser curvature is seen; the sickles shaped fold is the angle. Beneath it at the end of the antrum the pylorus appears.

observed penetrating ulcers in which the convergating folds were swollen and inflamed. Under treatment they quickly became shallower, smaller and the edge reddened (Fig. 10), a sign of healing, finally disappearing and leaving a very small gray scar.

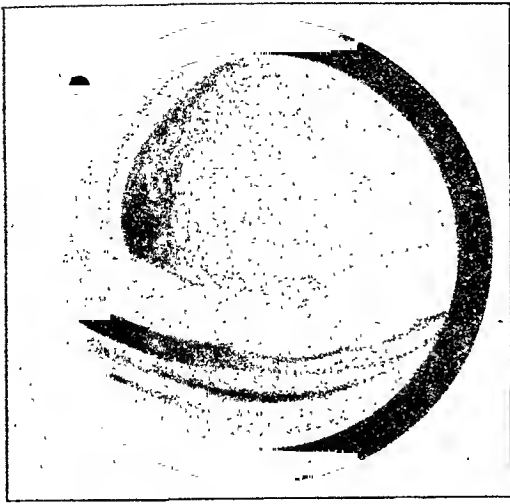


Fig. 6. Musculus sphincter antri, separating the cavity of the antrum (above) from the cavity of the body (in the lower part of the picture). The cordlike aspect is typical.

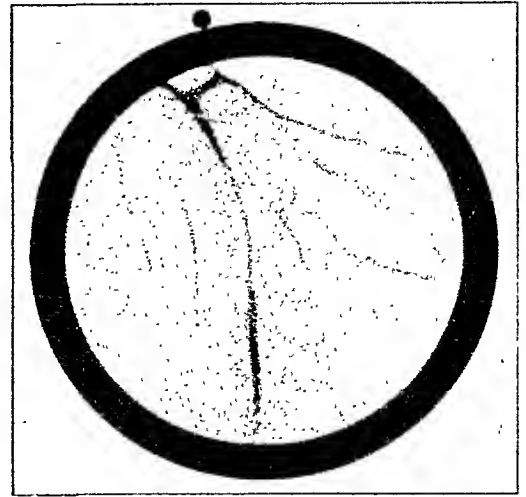


Fig. 8. Large longitudinal benign chronic gastric ulcer of the lesser curvature. (In the upper left quadrant just the margin of a second ulcer is seen).

At the present time the theory of the gastritic origin of ulcer is widely advocated, at least in Germany. We find gastroscopically that in many cases of ulcer the mucous membrane is identical with that seen in quite healthy persons. In many instances, the area surrounding the ulcer is distinctly swollen and reddened. In some cases, gastritic changes in the upper parts of the stomach are seen. The so-called "gastritis of the antrum" does not occur in cases of gastric ulcer. By this it becomes evident that our gastroscopical observations do not support the gastritic theory.

In Munich we found in 2% of the cases examined gastroscopically benign tumors which had not been found previously by X-ray relief technic. Fig. 11 shows the only case of *polypus ventriculi* which I have ever observed.

*Carcinoma* of the stomach shows the greatest variety of forms. The submucosal infiltrative lesions are seen as grayish rigid areas; the adenomatous types appear as nodular elevated tumors of various colors. The ulcerated lesions are seen as ragged, irregular, dirty brown or violet areas surrounded by a thick red wall. (Fig. 12).

Gastroscopy is of great value for the *differentiation of benign and malignant lesions*. The latter do not have the sharp edge and the yellow floor of the benign ulcer. Microscopic examination of the resected specimen has proved the exactness of the gastroscopic diagnosis in every instance thus far.

Gastroscopy also allows a better judgment with regard to the *operability of a tumor* than does X-ray examination. It enables one to observe the location of the lesion and the type and extent of involvement of the gastric wall, and thus to decide if it is likely whether or not a radical operation may be performed.

The most important field for gastroscopy is that of *chronic gastritis*. For thirty years this disease had disappeared almost completely from our conceptions of gastric pathology, although chronic inflammation in all the other mucous membranes is their most frequent disease. Gastroscopy has settled this question. There is no doubt that we find very often in patients, suffering from abdominal pains, changes in the mucous membrane which correspond with the inflammatory

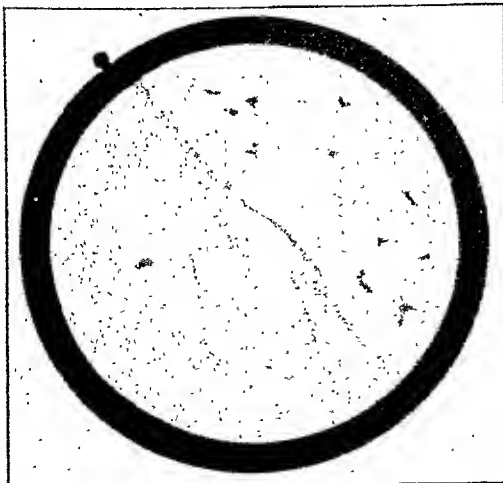


Fig. 7. Lesser curvature, showing numerous pigment spots and one small hemorrhage (paler, in the middle part). In this case, in the lower parts of the lesser curvature a chronic gastric ulcer was found.

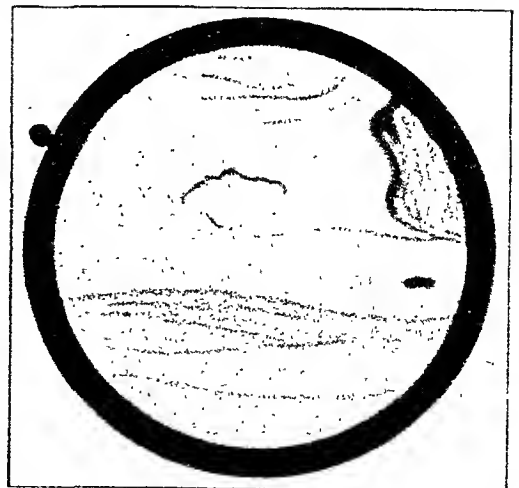


Fig. 9. Benign chronic gastric ulcer of the lesser curvature just above the angle. (At the right side the dark cavity of the antrum is seen, on the origin of the muscular sphincter antri a dark pigment spot. The ulcer occupies the middle of the picture. A part of its edge is undermined).

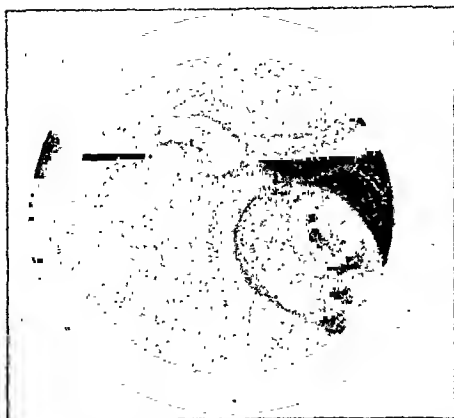


Fig. 10. Large benign chronic gastric ulcer, above the angle, healing. At the right side of the whitish ulcer is an edematous inflamed fold of the posterior wall. Under this the antrum with the dark hole of the pylorus appears.

processes of other mucous membranes. We should distinguish, in my opinion, three forms:

1. *Superficial gastritis*. Here red, apparently hyperemic spots of various sizes are seen, with layers of mucus and occasionally small erosions. Generally, this condition heals. It may develop, however, into the second form.

2. *Atrophic gastritis*. Here small gray-greenish spots are first observed. There are often hemorrhages, but erosions are rare. A complete atrophy may develop, as is indicated by the way in which the branching blood vessels of the submucosa may be seen through the mucosa. (Fig. 13). The relationship of atrophic gastritis to pernicious anemia and to the origin of tumors is an important consideration.

3. *Hypertrophic gastritis*. In this condition the mucous membrane is swollen, velvetlike, often verrucous, nodular, with creases and ulcerations. This hypertrophic ulcerative gastritis is a very severe condition and never heals completely. In one case, a fatal termination resulted from hemorrhages from very small ulcerations. The picture shown in Fig. 14 was found in a stomach with a gastric ulcer. A resection

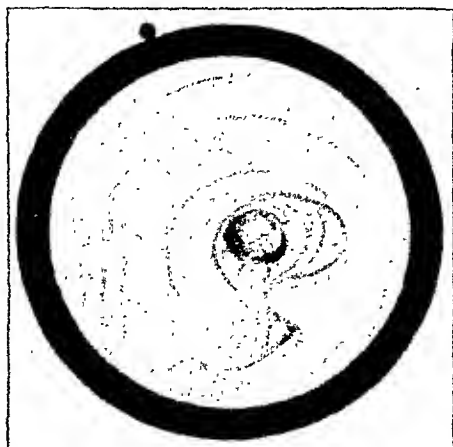


Fig. 11. Polyposus ventriculi. In the middle of the picture the pylorus and antrum are seen. In the body there are three small, stalactite-like prominences, which are benign polyps.

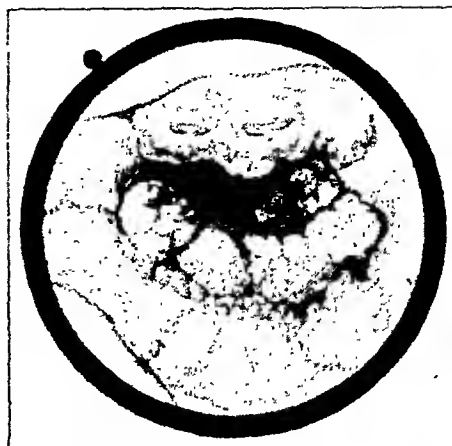


Fig. 12. Ulcerative carcinoma with thick reddened wall.

was made, and so it became possible to control the observed area microscopically. The fixation was made immediately after resection. Fig. 15 shows the microphotography with an extended interstitial cellular infiltration of the mucosa.

It is very interesting to observe *post-operative stomachs*. In those cases in which the new opening develops a pylorus-like rhythmic action, the patient remains healthy. If such an adaptation is missing, the patient develops pains which are apparently caused by either jejunal ulcer, which is seen often, or by a severe gastritis with a bad prognosis, or by silk sutures which are found to have cut through the mucous membrane. In Fig. 16 the opening into both loops of the intestinal coil is seen.

In conclusion, may I express the hope that this brief report will suggest the great value of gastroscopy in the various types of gastric disease.

#### SUMMARY

1. The invention of the flexible gastroscope has made it possible to view the interior of the stomach with safety and with relatively little discomfort to the patient.

2. Gastroscopical observation shows that the anatomical conception of the necessity of subdividing the cavity of the stomach in two parts is correct. An almost unknown formation, a high fold, between the

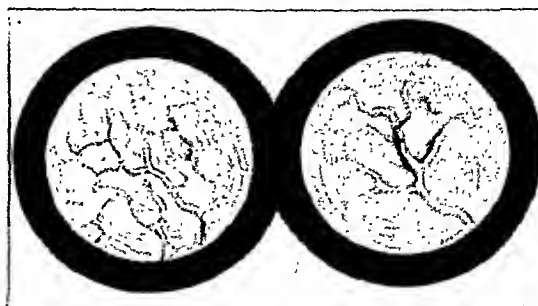


Fig. 13. Complete atrophy of the mucous membrane; at the left in a case of combined cord degeneration; at the right, in a case with purely psychoneurotic symptoms. The mucous membrane is so thin that a net of thick, prominent blood vessels is seen.

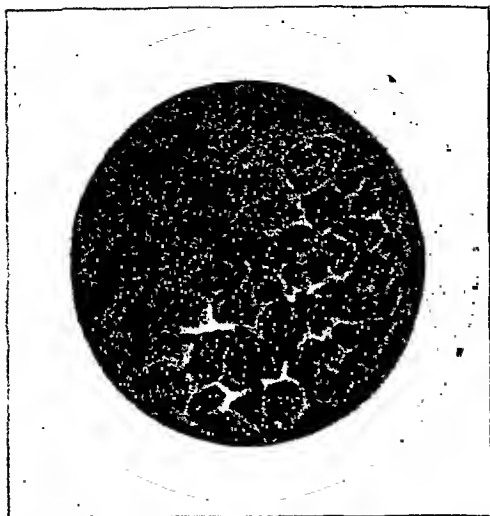


Fig. 14. Severe hypertrophic gastritis (observed in a case of gastric ulcer). The mucous membrane is swollen and nodular. At the left side a hemorrhagic spot is seen.

two cavities, the body and the antrum, is regularly seen.

3. In persons who suffer or who have suffered from gastric ulcer, hemorrhages and pigment spots of the gastric mucous membrane are often seen; these are not found in healthy persons.



Fig. 15. Microphotography of a section through the mucous membrane shown in Fig. 14. Extended cellular infiltration of the interstitium of the mucosa.

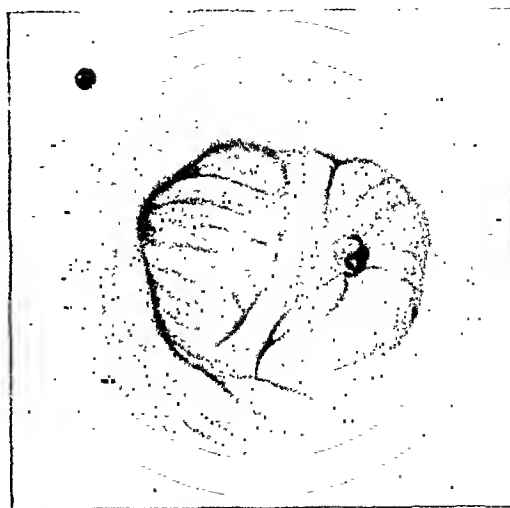


Fig. 16. Large operative opening between stomach and intestine. Both loops of the intestinal coil are seen; in the right one a peristaltic contraction can be observed.

4. Gastroscolical observations contradict the theory of the gastritic origin of gastric ulcer.

5. Gastroscoly allows the differential diagnosis of benign and malignant ulcer better than any other method.

6. Gastroscoly furnishes direct evidence of the progress of benign lesions and of the degree of involvement in cases of neoplasm.

7. Gastroscoly has rediscovered the frequency of chronic gastritis, which has to be considered as the most frequent lesion of the stomach. On the basis of our gastroscolical observations, it is subdivided into three great groups: superficial gastritis, atrophic gastritis and hypertrophic gastritis, which differ in their course.

8. Gastroscoly often reveals the reasons for complaints of patients after gastric operations. An ulcer or a very severe gastritis, or an irritation from silk suture may be found.

#### DISCUSSION:

DR. WILLIAM A. SWALM (Philadelphia, Pa.): You have just witnessed something which I believe will be the beginning of a new era in gastro-enterology. Dr. Schindler has studied this subject for many years and to one who has had the privilege of visiting him and watching him work in this field, it is more or less of a revelation.

True, he cannot see every lesion in the stomach. He cannot see the lesion just below the cardiac end of the esophagus, and without hesitation he tells us that he cannot observe an ulcer at the pylorus, although that may be worked out later, but in the rest of the stomach we saw the very things at which you were just looking.

In conjunction with the Doctors Jackson, especially Dr. C. L. Jackson, I have had the privilege of doing at least one hundred of these gastroscolies, and I have had the privilege of correlating gastro-enterological findings with gastroscoly. We heartily agree with Dr. Schindler that this method is here to stay.

DR. CHEVALIER JACKSON (Philadelphia, Pa.): When Dr. Swalm spoke about Dr. Jackson, he was referring to my associate, Dr. C. L. Jackson, and not to myself, though I have many times had the pleasure of looking through the flexible gastroscope, and can corroborate all the statements made by Dr. Swalm, and all of those made by the essayist. A few minor points still admit of discussion.

Dr. Schindler stated foreign body cases are not seen by the gastro-enterologist. That is absolutely true. Patients with foreign body in the stomach come to the laryngologist. It is curious, but such is the case. We have had four instances of foreign body in consultation with gastro-enterologists; in each instance the patient was the child of a gastro-enterologist, who brought the patient to us to remove the foreign body from the stomach.

I agree with the essayist on the matter of hemorrhagic spots and pigmented spots. We have been observing them for years and they do appear in an apparently otherwise healthy stomach, and yet we feel just as the essayist feels, that the stomach is not really normal.

I agree also with the essayist in regard to the differential diagnosis of malignant disease and ulcer, so far as the late cases are concerned. I think in the very early cases we will require biopsy in most instances to differentiate between ulcer and malignant disease, and also between benign growth and malignant disease, but that probably would apply chiefly to the early cases. I think no one is likely to mistake the appearance of a late and advanced carcinoma. The early ones, I think, will require biopsy.

I heartily agree with the essayist in regard to gastritis; his classification into the superficial, atrophic and hypertrophic, will do for the present; but there will be subclasses made to the number of about twenty-five or thirty different varieties of gastritis, classified on the basis of objective appearances, not on the basis of function.

Another point is that of the gastroenterostomy patient who has been disappointed with the results of gastro-enterostomy, and they are numerous; this is one field in which the gastroscope will help enormously in the relief of the patient. The patient who has had gastro-enterostomy done and has not been relieved of the symptoms, and perhaps has had symptoms added, requires local examination with the gastroscope.

I was disappointed that the essayist did not mention the subject of hernia of the stomach, trans-hiatal hernia of the stomach. That is one very important field, it seems to me, for the gastro-enterologist.

I do not feel that the gastro-enterologist should do as he has done in the past, abandon the stomach as part of it gets through the diaphragm, or abandon that part of the stomach that gets up through the diaphragm, and especially so because that part of the stomach is accompanied by symptoms that are gastric and not esophageal. Trans-hiatal hernia of the stomach is one of the relatively common things that has been overlooked.

I am not going to follow the essayist as to the cause of gastric ulcer. For forty-odd years, forty-five or more, I have looked on at the battle between the surgeon and the gastro-enterologist and the research worker as to what is the cause of gastric ulcer, and the end is not yet. There may be cases caused by gastritis, but they are probably cases that have other causes. It is still an open question. There is one point, however, on which I must differ with the essayist; an historical fact. The essayist said that when he took up the work in 1921, it had been abandoned all over the world. If he had not said "the world," I should not have disagreed with him. There was a small part of the world where there were done, between 1907 and 1921, over 1700 gastroscopies that are duly recorded. Many of them were incomplete gastroscopies, however, incomplete as compared to the work of the flexible gastroscope.

Another very slight point of difference with the essayist is in regard to technique, in regard to the use of a rubber guide attached to the distal end, a mandrin attached to the distal end of the rigid tube. To my mind that introduces a danger. He said that he found it less dangerous. I wish to issue a word of caution. When you are looking through an open tube, you can see what is ahead of you and, if you see tissue, you do not push on the tube. You wait until you find the lumen. To be safe one must find the

lumen before advancing the tube. You can not see through a rubber guide to find a lumen ahead, and, if the guide does not find it, you may go fatally astray. This refers to the open tube gastroscope.

In regard to the dangers: the dangers of any kind of gastroscope, are concerned altogether with the esophagus, not with the stomach. There is no danger to the stomach. Anyone competent to deal with the stomach at all, will never injure it with a gastroscope. There need be no hesitation whatever, but, as Dr. Swalm has pointed out, we must be sure that the esophagus is normal.

We can trust the roentgenologist in 95 to 96 per cent of the cases when he gives a negative opinion on the pathology of the esophagus, and 95 or 96 per cent is a very high average. I doubt if many other departments of medicine approach 96 per cent perfection, but there is that remaining element of 4 or 5 per cent against which we must be on our guard. Occasionally small lesions in the esophagus are overlooked.

I would not say that every patient ought to have an open tube gastroscope before he has the flexible gastroscope passed; but I think before putting down a flexible tube one ought to be sure no pathology exists in the esophagus; and sometimes the only way to be certain is with the open tube gastroscope.

We are using constantly in the Bronchoscopic Clinic, the flexible tube gastroscope described by the essayist, and we find it a great addition to endoscopy, the greatest addition that has been made for many years. But I wish to say that if the endoscopist is to do a gastroscopy he must have at his elbow, a gastro-enterologist to complete the diagnosis when the endoscopist gets through looking at the stomach, and also to do something for the patient after the diagnosis is complete. The endoscopist is merely a mechanic for the purpose of looking at the mucosa. When it comes to the functional tests and treatment of gastric disease he cannot measure up to the requirements of modern gastroenterology.

In conclusion, gastroscopy is an *addition* to and *not a substitute* for any other method of examination of the stomach. All other diagnostic methods are needed just as much today as they ever were. We have added to our means an additional method that will be invaluable in the study of the problems in general as well as the problems in the particular patient.

The gastroscopy will give the gastro-enterologist when he looks in the stomach, what he has never had before, living pathology, not the pathology of some previously dead patient on whom he has done an autopsy, but the living pathology in that particular patient, but it will not tell him anything about the function of the stomach. That remains just where it always has been, a matter for investigation by the gastro-enterologist, supplemented with gastro-intestinal study by the roentgenologist.

DR. EDWARD B. BENEDICT (Boston, Mass.): I want to compliment Dr. Schindler very highly for his work on gastroscopy and the development of the flexible gastroscope; I think we owe a great deal to him in the diagnosis of stomach conditions.

For the past two years at the Massachusetts General Hospital in Boston we have been conducting frequent gastroscopic examinations in connection with the Gastro-Intestinal Clinic, and are finding it a very useful procedure.

I have been interested in gastroscopy from a surgical standpoint, and Dr. Chester Jones from a medical standpoint has also been very much interested.

(Slide) This is a carcinoma of the stomach, a typical nodular growth that was well seen by the gastroscope, an advanced condition which was also seen by X-ray.

(Slide) This is a polypoid tumor of the stomach which proved on removal to be a malignant adenomatous polyp.



(Slide) In regard to early carcinoma, the gastroscope may make the diagnosis before the X-ray. This patient, a forty-five-year-old man, had gastric complaints for three months. The X-ray showed enlarged rugae and the roentgenologist made a diagnosis of gastritis on that basis. We may, however, have hypertrophic rugae without gastritis, or gastritis without hypertrophic rugae.

Gastroscoy in this case showed many large elevations and depressions which suggested malignant disease very definitely. The patient was not operated on at that time, but did not respond well to treatment, and four months later the X-ray suggested malignant disease. Operation was done and the lesion proved to be inoperable carcinoma.

(Slide) This is a benign gastric ulcer as seen by gastroscopy. The rugae may be seen characteristically converging toward the lesion. As Dr. Schindler pointed out, the smooth margins and clean-appearing base are typical of a benign lesion. A malignant lesion would show nodular margins and a dirty base. I think in these cases the gastroscopic differentiation is of importance.

(Slide) Then, hypertrophic gastritis; we have the verrucous, warty appearance of the mucosa as contrasted to the smooth rugae in the normal stomach.

(Slide) The bleeding cases: This patient complained of gastro-intestinal bleeding. The gastric X-ray and barium enema were entirely negative and the source of the bleeding was revealed by gastroscopic examination as coming from the eroded area seen on the slide.

(Slide) Then we have atrophic gastritis seen especially in pernicious anemia with the blood vessels clearly seen shining through a very pale, thin mucosa, entirely different from the normal.

(Slide) That particular patient also had a benign polyp clearly seen through the gastroscope. The X-ray had questioned malignant disease. Gastroscoy made the diagnosis almost certainly a benign polyp, frequently associated with pernicious anemia.

(Slide) After liver therapy and operative removal of the polyp the color improved and the normal rugae began to return, the appearance in general returning to normal.

In conclusion, I want to emphasize the importance of the gastroscope in diagnosis and localization of early

carcinoma, in benign ulcer of the stomach, and particularly in gastritis.

DR. RUDOLF SCHINDLER (closing discussion): I think that the Chairman would not be very satisfied if I were to discuss all these questions which have been brought up in discussion. They include, really, the whole pathology of the stomach. I wish to thank you all for the great interest which has been shown in this paper, and especially I want to thank Dr. Chevalier Jackson.

When I read the literature, I am accustomed to read over and over two classical papers, those of Mikulicz in 1881, and Chevalier Jackson in 1907. They were the pioneers. The observations of 1907, made through an open tube, by Chevalier Jackson are astonishing, and it would be difficult for me to make them in this way. That Dr. Jackson now has accepted the method with the flexible tube, and that he is able to follow in the new ways, shows how young he still is.

One remark that he made was of great interest to me, about the classification of the gastritis, because I was writing a paper on this subject in collaboration with Dr. Ortmyer, which will appear soon. Classification is a difficult problem. Shall gastritis be subdivided in accordance with only the gross gastroscopies as Moutier in Paris does. I have the impression it should not. The best way at this moment is to follow the development of the different pictures, and after the course and prognosis to subdivide gastritis in these three forms which I have described. Perhaps we can later subdivide gastritis according to the etiology, but we are not yet at that point.

I agree with Dr. Swalm completely that gastroscopy allows gastro-enterology to enter a new era, the era of morphologic diagnosis, naturally not without X-ray. X-ray examination and gastroscopy are cooperative methods. They help each other.

The question is: Who will carry out the gastroscopies? You know that in Germany gastroscopy is a routine method of the gastro-enterologist. I don't know whether it will be so in this country. I was happy when a young physician of Jacksonville, Florida, told me that after what he had seen he believed that the gastroscope will in a short time be part of the equipment of every gastro-enterologist. That is my opinion also.

## Bacteriological Findings in Disease of the Biliary Tract\*

### An Improved Method of Obtaining Cultures of Bile by Duodenal Drainage

By

JOHN RUSSELL TWISS, M.D.

and

CHARLOTTE H. PHILLIPS, M.D.

NEW YORK, NEW YORK

**E**VIDENCE of biliary tract infection obtained by duodenal drainage is of diagnostic value only if the specimens of bile procured are free from extraneous contaminations. As shown by Hanssen and Yurevich (1), many varieties of organisms cultured from duodenal bile are not found in the biliary tract at operation. It is the purpose of this paper to indicate the sources of these contaminating organisms,

and to describe a method of taking duodenal cultures which for the past 2 years has given results more in accordance with the conditions actually found at operation than those obtained by methods heretofore in use.

The actual incidence of contamination was shown by Hanssen and Yurevich (1) in a complete bacteriological study of 104 operative patients. Evidence of infection was found in some part of the biliary tract in 33% of the cases, 20% of the gall bladder bile cultures being positive. A single infecting organism was found in 95% of the cases. Forty-eight of these

\*From the Departments of Medicine and Surgery of the New York Post Graduate Hospital.  
This work has been aided by a grant from the Oliver Rea Fund.  
Submitted July 8, 1935.

patients had sterile drainages before operation, positive cultures were obtained in 69% of these drainages. This finding compares favorably with other published reports. However, only 33% of these patients showed infection at operation. 42% of those whose biliary tracts were sterile at operation had a mixed growth of organisms in the drainage bile.

An analysis of possible sources of contamination suggests the necessary manipulation of the duodenal tube. Contamination may occur at the syringe end of the tube by contact with unsterile fields, hands, or by

ers the fasting stomach sterile. Patients having a normal or increased acid content usually show no organisms, those with achlorhydria almost invariably have positive gastric cultures. According to Bartle and Harkins (2), only gastric contents with free hydrochloric acid of over 20° have bactericidal power.

The third likely source of contamination in performing a drainage of the biliary tract is the mouth and throat, for as many investigators have shown the tonsils, teeth, and pharynx harbor innumerable organisms. Boardman (3) has shown that attempts at

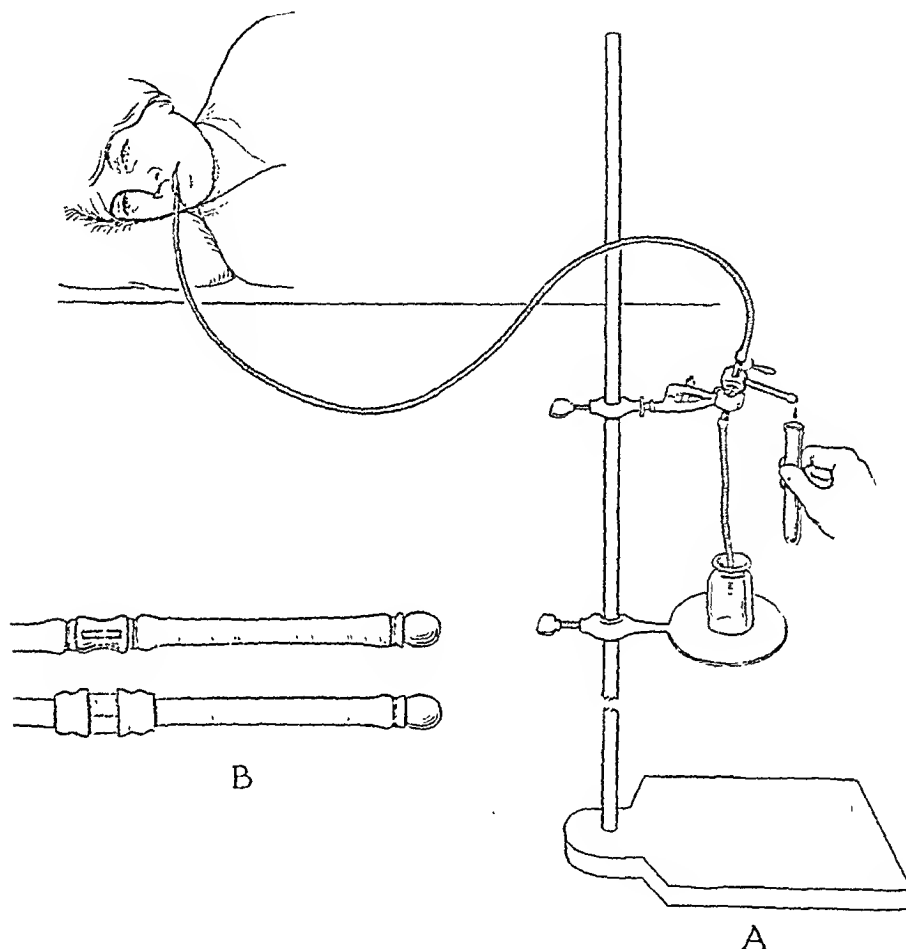


Fig. 1. The single drainage tube, showing: A. The three-way stop-cock and bile container, supported by a ring-stand. Bile for culture is obtained in a test tube from the side-arm, the bile being diverted for this purpose when necessary. B. The metal bucket and leader of the tube, with and without the keratin-coated capsule in place.

a syringe with contaminated tip. With the usual method of drainage contamination may occur through the bucket end of the tube by the introduction of infected materials from the mouth, throat, or stomach. Finally, contamination may result from inadequate sterilization of the drainage tube, bile containers, or solutions.

Another probable source of contamination is the stomach. Organisms from the food, saliva, tonsils, teeth, sinuses and various parts of the upper respiratory tract are unquestionably swallowed. The presence of the free hydrochloric acid, plus possibly the action of the pepsin, normally constitutes a protective mechanism which destroys swallowed organisms and rend-

sterilization of the mouth have had no apparent effect in reducing the bacterial flora, cultures taken before and after these procedures showing identical growths.

There is obviously a discrepancy between the sterile cultures or the single type of organism usually found in the biliary tract and the many types of organisms which have been commonly reported as present in the duodenal bile. Various methods of obtaining sterile cultures of duodenal bile have been described, notably that of Lyon (10). MacNeal and Chace (5), as well as Whipple (6) have used tubes sealed off to preserve sterility. A small tube for sterile cultures, contained in an outer tube, has been devised by Buttiaux. There are, however, inadequate data based upon comparative

bacteriological studies and findings at operation to confirm the practicability of these methods. A different method has been devised and has been in use for the past two years, with very satisfactory results, in the Clinic for Diseases of the Liver and Biliary Tract of the New York Post-Graduate Hospital.

### METHOD

The principle of our closed or encapsulated drainage in eliminating contaminations is the sealing off of a Twiss duodenal tube (7) by means of a keratin-coated gelatine capsule (Figure 1). The usual type of single Twiss tube may be used when its position can be checked by the use of the fluoroscope. The double tube as shown in Figure 2 is, however, an advantage, for

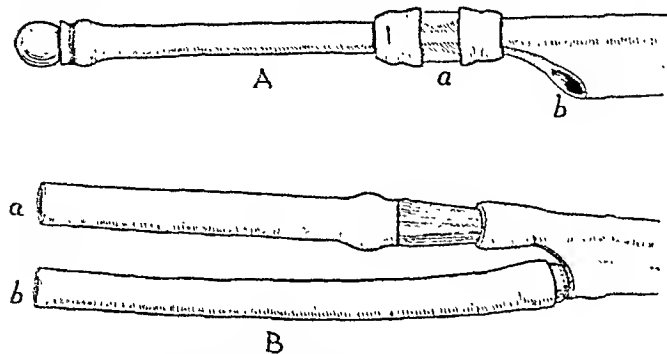


Fig. 2. The double duodenal tube: A. Bucket end of tube, showing (a) metal bucket covered by keratin-coated capsule, which is held in position by wide rubber bands. (b) opening of pilot tube, for the purpose of obtaining gastric and bile specimens not cultured. B. Syringe end of tube, showing (a) tube through which bile for culture is obtained. (b) pilot tube.

one tube serves as a pilot tube for the taking of gastric or biliary specimens and for determining the position of the tube in the duodenum as shown by the character of fluid obtained, thus obviating the need of a fluoroscope. A further advantage of this arrangement is in showing, at all times, the type of bile being discharged, so that cultures may be taken when indicated. The second tube, which is for the purpose of procuring bile for culture only, has the slotted metal bucket, over which the capsule is held in place by wide rubber bands. The tube and rubber bands are sterilized by boiling, the capsule is sterilized in absolute alcohol and applied with sterile precautions. If the double tube is not available, or its passage through the stomach is difficult on account of a persistent pylorospasm, a single encapsulated Twiss tube is used.

That the sterile capsule maintains its integrity until reaching the alkaline medium of the duodenum has been demonstrated in the following way: The duodenal tube was filled with barium solution and the capsule applied. The tube was then swallowed by a patient and passed to the duodenum, as checked by fluoroscopic inspection. A roentgenogram taken at this time showed the barium retained in the tube. The capsule was then removed by pressure applied by a syringe, a second roentgenogram showed the barium distributed in the duodenum.

A further attempt has been made to eliminate contamination at the syringe end of tube. A three-way stop-cock (8) is attached to the end of the duodenal tube, the stop-cock and bottle for bile being supported by a large ring-stand (Figure 1). The drainage of

bile and the introduction of stimulating fluids is conducted through the direct pathway. Cultures are taken from the side-arm only, the bile being temporarily diverted for this purpose. Both the tip of the side-arm and the mouth of the sterile test-tube are flamed before taking the cultures.

The drainage is done with the patient having had no food for at least 12 hours; the mouth and throat are sprayed with 10% silver nucleate, followed by a gargle of the same solution, before passing the tube. After the single tube is passed into the duodenum, its position is verified by fluoroscopic inspection. The capsule is then removed by the instillation of hot sterile water by a syringe, the duodenum being thoroughly lavaged with sterile water before beginning the drainage. The complete equipment and its sterilization, as well as the method of performing the drainage, are elsewhere described (9).

Specimens of bile are collected before and after stimulation with sterile magnesium sulphate or olive oil, the dilute or duodenal bile and most concentrated specimens only being cultured. Bacteriologic studies of bile specimens were made under the direction of Dr. Adele Sheplar of the Department of Bacteriology. Details of the laboratory methods employed may be found in our Clinic Manual (9).

### RESULTS

For the purposes of illustrating the results of this type of drainage a series of 165 consecutive drainages is reported on 50 patients referred to this clinic with a tentative diagnosis of disease of the gall bladder. Fifty patients were drained 87 times by the closed or encapsulated method, 31 of the same patients were drained 78 times by the open or usual method. Throat cultures were taken in 20 patients immediately preceding drainage by both the open and closed methods.

A study was made of the organisms found in the throat cultures and in the duodenal bile specimens obtained by both methods, the results are shown in Table 1. The usual or open method gave sterile cultures in

TABLE I

|                                                                    | Throat | Open Method<br>(15 drainages)<br>Duodenal | Throat | Closed Method<br>(18 drainages)<br>Duodenal |
|--------------------------------------------------------------------|--------|-------------------------------------------|--------|---------------------------------------------|
| Total no. variety of organisms in positive cultures                | 52.    | 31.                                       | 64.    | 22.                                         |
| Average no. types of organisms per culture                         | 3.5    | 2                                         | 3.5    | 1.2                                         |
| Sterile cultures, %                                                | 0      | 13%                                       | 0      | 38%                                         |
| Duodenal cultures showing organisms similar to those of the throat |        | 60%                                       |        | 23%                                         |

Table I. A comparison of the bacteriological findings of the throat and duodenal bile, as obtained by the open or usual method and the closed or encapsulated method.

13% of the drainages, organisms similar to those found in the throat were present in 60%. In the same patients, drainage by the encapsulated tube method showed sterile cultures in 38% of the cases, only 23% had organisms similar to those of the throat. These results indicate that with the encapsulated method fewer contaminating organisms from the throat and mouth are found in the duodenal bile.

We have also made a study of a series of patients, who had for the most part repeated drainages and

in some cases repeated throat cultures (Table 2). Patients drained by the open method, were found to have sterile cultures in 10% of the cases, only one or

TABLE II

|                                       | Throat | Bile        |               |
|---------------------------------------|--------|-------------|---------------|
|                                       |        | Open Method | Closed Method |
| No. of patients                       | 33     | 30          | 50            |
| No. drainages                         |        | 78          | 87            |
| Sterile, %                            | 0      | 10          | 34            |
| 1-2 types of significant organisms, % | 10     | 22          | 32            |
| Total Significant Findings, %         |        | 32          | 66            |
| Mixed growths (3 or more organisms) % | 90     | 68          | 34            |

Table II. Percentage of patients showing sterile and positive cultures of the throat and duodenal bile, as obtained by the open and the closed or encapsulated methods.

two types of significant organisms were present in 22%, mixed growths of 3 or more organisms occurred in 68% of the patients. The same patients drained by the encapsulated tube method showed sterile cultures in 34% of the cases, the per cent of significant types found at operation rose to 32%, mixed growths occurred in only 34%.

The varieties of organism found in the throat and duodenal bile cultures are shown in Table 3. The pre-

TABLE III

|                             | Throat | Bile        |               |
|-----------------------------|--------|-------------|---------------|
|                             |        | Open Method | Closed Method |
| No. patients                | 20     | 30          | 50            |
| Sterile                     | 0      | 10          | 34            |
| Non-hemolytic streptococcus | 100    | 66          | 32            |
| Micrococcus catarrhalis     | 70     | 36          | 10            |
| Hemolytic streptococcus     | 25     | 3           | 2             |
| B. influenzae               | 20     | 0           | 0             |
| Green streptococcus         | 15     | 6           | 2             |
| Staphylococcus albus        | 10     | 40          | 16            |
| Diphtheroids                | 10     | 20          | 2             |
| Pneumococcus                | 10     | 0           | 0             |
| Friedlander groups          | 5      | 3           | 4             |
| Diplococcus (unclassified)  | 0      | 6           | 2             |
| B. Proteus                  | 0      | 10          | 6             |
| B. Coli communior           | 0      | 16          | 6             |
| B. acidii lactici           | 0      | 13          | 8             |
| Lactis aerogenes group      | 0      | 20          | 12            |
| Yeasts                      | 0      | 20          | 14            |
| Staphylococcus aureus       | 0      | 23          | 18            |

Table III. Percentage of patients showing sterile cultures and various types of organisms in the cultures of the throat and in the cultures of bile obtained by the open and closed methods.

dominating organisms of the throat are seen to be the streptococcus of the non-hemolytic, hemolytic, and green types, as well as the *M. catarrhalis*. There is a relatively high incidence of *B. influenzae*. Patients drained by the open method showed predominately these organisms, for example the non-hemolytic streptococcus, *Micrococcus catarrhalis*, *staphylococcus albus*, and diphtheroids occurred from 2 to 10 times as frequently as in those patients drained by the encapsulated method. Patients drained by the encapsulated method show a decreased incidence of all organisms. The non-hemolytic streptococcus was again found to predominate, most of the other organisms found in

higher percentages are of types found in the biliary tract at operation.

In a further study, a series of gastric cultures was taken immediately preceding drainages by the open method. The same types of organisms were found in the stomach as in the throat. Staphylococci, however, which were seldom found in the throat cultures, were usually present in the gastric contents with diminished or absent free hydrochloric acid. In all patients one or more types of bacteria found in the gastric specimens were present in the duodenal bile.

## CONCLUSIONS

The results of these investigations indicate that the organisms found in the biliary tract and not usually in the stomach or throat are found in higher incidence and more frequently in pure culture in the duodenal bile obtained by means of the encapsulated method here described. These include the *B. coli communis*, *B. acidii lactici*, the *lactis aerogenes* group, *B. proteus*, *B. Welchii*, and *B. typhosus*. On the other hand drainage bile obtained by the usual or open method was found to show more frequently mixed growths of those organisms indicating contamination, such as the *micrococcus catarrhalis*, Friedländer groups, diphtheroids, diplococci, and pneumococci. For these reasons we consider all findings more reliable when the bile is obtained by the encapsulated method.

A further study is in progress at the present time in which a series of patients with biliary tract disease are being drained preoperatively by the encapsulated method. The results of the cultures are then being compared with the bacteriological findings at operation. A report of this investigation will be made at a later date.

## SUMMARY

1. Bacteriological studies of the biliary tract at operation in practically all cases have shown sterile cultures or a single type of organism.
2. Cultures of bile obtained by means of the duodenal tube have shown in most cases a variety of organisms, many of which are found in the mouth, throat, and gastric contents.
3. Specimens of duodenal bile obtained by present methods in many instances are contaminated and cultures can not be considered diagnostic of biliary tract infection.
4. A method of taking sterile cultures of duodenal bile by means of an encapsulated tube is described. This method has given a higher percentage of sterile cultures and a higher incidence of pure cultures of bacteria significant of biliary tract disease than the one previously used. Studies have further shown a lower incidence of mixed growths of organisms, especially in those types of contaminating organisms found in the throat and stomach.

The Authors are indebted to Dr. Carl H. Greene for assistance in the preparation of this article, as well as for suggesting the use of the double duodenal tube.

## REFERENCES

1. Hanssen, E. C., and Yurevich, A.: Bacteriological Findings in Disease of the Biliary Tract. A Comparison of Operative Findings with those of Non-Surgical Drainage of the Biliary Tract in 104 Cases. *Am. Jour. Dig. Dis. and Nutrit.*, Vol. 2, No. 8, pp. 460-466, Oct., 1935.
2. Bartle, H. J., and Harkins, V. M. D.: The Gastric Secretion: Its Bactericidal Value to Man. *Am. Jour. Med. Sci.*, 169:373, March, 1925.
3. Boardman, W. E.: A Study of the Bacteriological Findings in the Lyon-Meltzer Test. *Am. Jour. Med. Sci.*, 167:S74, June, 1924.
4. Lyon, B. B. V.: Non-Surgical Drainage of the Gall Tract. Lea & Febiger, Philadelphia, 1923.
5. MacNeal, W. J., and Chace, A. F.: A Contribution to the Bacteriology of the Duodenum. *Arch. Int. Med.*, 12:178, 1913.
6. Whipple, Allen O.: The Use of the Duodenal Tube in the Pre-Operative Study of the Bacteriology and Pathology of the Biliary Tract and Pancreas. *Annals of Surg.*, 73:556, May, 1921.
7. Twiss, J. R.: A New Type of Duodenal Tube Tip. *Am. Jour. Med. Sci.*, 185:109, Jan., 1933. (Tube made by the Sklar Mfg. Co., Brooklyn, N. Y.).
8. Made by the George Pilling Co., Philadelphia, Pa.
9. Carter, R. F., Greene, C. H., and Twiss, J. R.: Diagnosis and Treatment of Diseases of the Biliary Tract: Methods Employed in the Clinic for Diseases of the Liver and Biliary Tract of the N. Y. Post-Graduate Hospital, 1934.
10. Lyon, B. B. V.: The Bacteriology of Bile Obtained by Duodenal Tube Drainage. *J. Lab. and Clin. Med.*, 17:583, 1934.

# A B S T R A C T S

ABELL, IRVIN.

*"The Diagnosis and Treatment of Duodenal Ulcer."*  
*South. Med. Jour.*, 28:138-141, Feb., 1935.

In an unbiased and thorough manner the Author presents the difficulties encountered in the diagnosis and treatment of duodenal ulcer, utilizing his own case records for his observations.

The diagnosis is frequently obscure in the absence of many of the classical symptoms: hunger pain with food relief; fullness, discomfort, or sour eructations some time after ingestion of food; seasonal variations; hemorrhage in stool or vomitus; and vomiting of food or gastric secretion when pyloric obstruction occurs. Actual pain may be absent or very acute and severe. The symptoms may be of such short duration and with such long periods of remissions that they may be attributed entirely to dietary indiscretion. Evidences of gross hemorrhage will be lacking in 80% of the cases. Since, however, all the later complicated pathological changes in the ulcer and surrounding tissues have their origin in what is first a simple ulcer thorough examination, including laboratory and X-ray studies are indicated in all cases of "stomach trouble."

The treatment is primarily medical, consisting of diet, antacid medication, elimination of focal infection and institution of other general health measures. Persistence and adequacy of this regimen are essential.

The Author reserves operation for patients presenting one or more of these conditions: perforation, repeated or long continued hemorrhage, pyloric obstruction, and intractable chronicity. In the majority of cases perforation is best treated by simple closure of the leak without additional plastic procedures. Single massive hemorrhages rarely require operation but when hemorrhage of any kind does demand surgical treatment the ulcer should be destroyed. Simple pyloric obstruction is well cared-for by gastroenterostomy but in the small percentage of those cases showing multiple, extensively-calloused or posteriorly-placed ulcers, with perforation into or fixation to the pancreas, resection of the duodenum and pylorus seem indicated. Those intractable chronic cases best are treated by pyloroplasty with excision of the ulcer or gastroenterostomy with destruction of the ulcer. The radical ablation of the acid-bearing portion of the stomach seems an unnecessarily extensive operation and the continued subsequent absence of hydrochloric acid should make one consider the possibility of serious secondary changes resulting from disturbed body chemistry.

In spite of proper surgical treatment of the ulcer, including also the removal of an infected gall bladder or appendix, and proper postoperative diet, the patient is a potential ulcer prospect for life. Recurrence is probably due to our incomplete knowledge of the etiology. Team

work by internists, surgeons, pathologists, research workers and roentgenologists is essential for the solution of the problem.

J. Duffy Hancock, Louisville.

GRAY TURNER.

*Recent Advances in the Treatment of Carcinoma of the Esophagus From the Surgical Aspect.* *Jour. of Laryngol. and Otol.*, XLIX, pp. 297-311, May, 1934.

The patient in this case was a man fifty-eight years of age, who complained of serious difficulty in swallowing of eight weeks' duration. Solid food appeared to stick at the lower end of the sternum, and he could swallow only foods of the consistency of porridge. He had lost 42 pounds in eight weeks. Roentgenoscopic study revealed the characteristic shadow of a neoplasm in the middle of the esophagus.

Gastrostomy was performed and exploration failed to reveal secondary deposits in the liver. Twenty-three days later, the abdomen was re-opened through an incision in the median line which was carried high up between the left costal margin and the xyphisternum. The left lobe of the liver was detached from the diaphragm and turned to the right. The peritoneum over the esophagus was incised and enucleation was commenced with the forefinger introduced through the hiatus and worked up as far as possible around the tube. When no further separation could be accomplished, the abdominal region was covered with sterile towels and the field of operation was transferred to the neck. A transverse or oblique incision was made just above the left clavicle, dividing the sternomastoid muscle. The cervical esophagus was exposed by blunt dissection and separated as far down as the finger could reach; the esophagus was then surrounded by a silk ligature at as low a point as it could be tied. It was cut across with the cautery and the lower end and parts around freely smeared with bipp (bismuth iodoform paraffin paste). The proximal end, which had been controlled by a light clamp, was then brought out of the incision. A return was made to the abdomen and traction made on the esophagus. The esophagus, including the neoplasm, was freed from its bed, ligatured at the cardia, and cut away from the stomach. The stump was securely buried by purse-string sutures. The open esophageal tunnel in the diaphragm was repaired by suturing the left lobe of the liver over its mouth and the abdomen was closed.

Nine weeks after gastrostomy, in a series of operations, a new esophagus was constructed by making a tube from the skin over the front of the chest, and the gap between the skin tube and stomach was bridged by an isolated loop of jejunum. Six weeks after the last stage of the operation, the gastrostomy tube was removed and the patient was able to take all food by mouth.

Porter Vinson, Rochester, Minn.

## SECTION II—*Experimental Physiology*

### V. The Effects of Drugs on the Motility of Isolated Segments of the Intestine of Man \*

By

J. ARNOLD BARGEN, M.D.†

and

JOHN S. GUTHRIE, M.D.‡  
ROCHESTER, MINNESOTA

IN recent years, this Clinic has offered a unique opportunity for intensive study of functions of the large intestine. Patients who have had various kinds of intestinal disorders have been segregated on one floor of a hospital, under combined medical and surgical management. In this way, fifty to seventy-five patients, most of whom had disease of the colon, have been under observation the year around. Some of them consented to the performance of certain harmless, painless investigations, by which we hoped to learn facts which would be of benefit to them and to others. Consequently, many problems for clinical research have suggested themselves.

These patients were under the care of specially trained nurses and workers. This fact has been of great help in the execution of our research. This is the fifth report of a series of problems. The next study, now well under way, concerns the functions of the small intestine of colectomized patients. Colectomies have been done only for extensive polyposis or advanced chronic ulcerative colitis with serious complications. The results will be reported in the near future.

#### REVIEW OF PREVIOUS STUDIES

Members may recall that, at the meeting of this Association, in 1929, results of the first series of investigations were reported. These investigations were made on dogs. They established the fact that, in dogs, selective absorption and excretion of various drugs took place in the isolated colon. The colon of the dog was isolated by sectioning the distal part of the ileum, and the colon, as near to the anus as possible, and making end-to-end anastomosis of the proximal part of the ileum and the distal part of the colon. The distal end of the ileum was then brought to the outside of the abdominal wall, on the right side, and the proximal end of the colon was treated likewise on the left

side, thus leaving the colon in the abdominal cavity, with nerve supply and blood supply intact.

The second and third studies concerned the motor and secretory activities of these isolated segments of colon. It was established that secretion of mucus is a normal function of the mucosa of the bowel and that mucus serves as a lubricant and protects against penetration of harmful bacteria. There was a strong suggestion that the mucus acted as a regulator of absorption. It was found that the amount of mucus secreted varies directly with the amount of colonic irritation; the source of irritation may be central as well as peripheral. Great loss of nitrogen occurs by excessive secretion of mucus. Mucus is not a product of inflammation.

The motor activity of segments of the colon varies. In the cecum, there is mixing and churning, and thus absorption is aided. In the distal portion of the dog's colon, the activity is largely one of propulsion.

With these studies on dogs as a background, similar studies on man have been undertaken. Some have been completed. The fourth study was reviewed in "*Surgery, Gynecology and Obstetrics*," March, 1935. It concerned the absorption and excretion of various substances in isolated segments of the colon of man.

A surprising amount of conflicting experimental evidence exists concerning absorption of substances, other than water, by the large intestine. Colostomized patients are ideally suited to elimination of the usual fallacies inherent in investigations of colonic absorption. Instead of studying the colon of carnivorous or herbivorous animals, as has been done in the past, we could make observations on the isolated colon of omnivorous man. The divided colon has the added advantage of preventing error from regurgitation of the clyisma into the absorbing ileum. Short distal segments can be thoroughly evacuated, thereby eliminating any errors attributable to failure to recover unabsorbed fractions, and finally, such segments can be cleansed, thus preventing error attributable to fermentation by bacteria.

By a study of such isolated portions of the colon of man, it was found that even in the distal seg-

\*Presented at the 34th Annual Session of the American Gastroenterological Association, Atlantic City, N. J., June 10-11, 1935.

Approved by the Publications' Committee of the Association.

†Division of Medicine, The Mayo Clinic.

‡Fellow in Surgery, The Mayo Foundation.



ments there is absorption of methylene blue, atropine, sucrose, arsenic as neoarsphenamine and glucose. Distal segments of the colon of man do not excrete methylene blue, glucose, or sucrose. Arsenic, as "trep-arsol," is excreted by the distal segments.

#### PRESENT STUDY CONCERNING THE EFFECTS OF DRUGS ON MOTILITY

Many drugs have been used in the past to combat and prevent postoperative intestinal distention, such as that which occurs with paralytic ileus from various causes. So far, knowledge regarding the ability of drugs, as extract of the posterior lobe of the pituitary body ("pituitrin"), physostigmine, acetylcholine, or "peristaltin," to influence intestinal tone and motility, has been founded principally on the results of experimentation with animals and on impressions acquired by clinical observations of the effects produced following administration of these drugs to patients affected with postoperative intestinal distention.

We undertook to evaluate the effects of these drugs on patients on whom colostomy had been performed. Patients who have undergone colostomy or ileostomy, at various levels, afford opportunities to study accurately the action of these drugs on intestinal segments. The intestinal stomas in the cases studied, had been made as steps preliminary to eradication of intestinal neoplasms, so that in each case ample normal colon was at hand after surgical resection.

For our experiments, patients were selected whose intestinal motility had been disturbed to the least possible extent. Hence, they were chosen with the thought that colostomy had not been performed longer than two weeks before the experiment was undertaken. The patients were all in excellent general condition and their bowels and colonic stomas were functioning well. No interference with intestinal function had taken place for several days before each experiment. During each experiment, the patient was supine on a couch, in a room that had been especially set aside for the carrying out of this study. Hence, the subject was free of extraneous influences which might cause reflex nervous irritation.

The apparatus used for these experiments was a closed air-balloon system, connected with a tambour and recording lever, this, in turn, writing with an ink point on smooth kymographic paper fastened to a revolving drum.

The drugs, whose action on the intestine of man we investigated, were (1) surgical pituitrin, (2) physostigmine sulphate, (3) "peristaltin" (Ciba), or soluble extract of cascara sagrada, grains  $2\frac{1}{2}$  (0.15 gm.) per ampoule, prepared for hypodermic use, and (4) acetylcholine. All the drugs were administered intramuscularly. The effect of each drug on various segments of the intestine was recorded.

**THE TRANSVERSE COLON.**—*Pituitrin*: After administration of pituitrin, powerful contractions of the transverse colon began within three to five minutes. These contractions occurred every three to five minutes, and the effect of the pituitrin lasted for forty-five to ninety minutes.

*Physostigmine*: Doses as large as  $1/35$  grain (0.0018 gm.) caused no effect on this segment of colon.

*"Peristaltin"*: In some cases,  $2\frac{1}{2}$  grains (0.15 gm.) of this drug caused slight and irregular contractions. The contractions occurred every one and a half

minutes to seven minutes, for an hour. At other times no effect from this drug was recorded.

*Acetylcholine*: Doses as large as 6 grains (0.4 gm.) caused no effect on this segment of colon.

**THE SIGMOID COLON.**—*Pituitrin*: This drug caused, on the sigmoid, reactions identical with those which it had exhibited on the transverse colon.

*Physostigmine*: Small to medium-sized contractions resulted from administration of this drug; the contractions occurred every one to eight minutes, for an hour.

*"Peristaltin"*: A few small contractions occurred at irregular intervals.

*Acetylcholine*: Slight elevation of tone of the sigmoid occurred between six and nine minutes after administration of this drug, and small contractions occurred at irregular intervals for about forty-five minutes.

**TERMINAL PART OF ILEUM AND SIGMOID COLON.**—With balloons in the terminal part of the ileum and in the sigmoid colon of a single individual, simultaneous recording of contractions could be made.

*Pituitrin*: Contractions occurred simultaneously, in both sections of bowel, every one and a half to three minutes.

*Physostigmine*: On some occasions, no effect on the ileum could be recorded after administration of this drug; on others, increased ileal tone occurred, associated with small to medium-sized contractions every one and a half minutes to five minutes. The contractions occurred, although they gradually decreased in magnitude, for 105 minutes. In the sigmoid, slight contractions occurred every two to four minutes, beginning about ten minutes after administration of the drug.

*"Peristaltin"*: On some occasions, no effect was observed on either the ileum or the sigmoid; on others, when administration of the drug was repeated, and in similar amounts, thirty minutes after the initial dose had been given slight increase in ileal tone occurred, but no effect on the sigmoid was noted.

*Acetylcholine*: Slight increase in tone of the ileum occurred for twenty minutes.

#### CONCLUSIONS

1. These experiments would compel the conclusions that pituitrin alone is a constant motor stimulant of the large and the small intestine of man. It increases motility without effect on intestinal tonus. Its action is rapid and powerful.

2. The action of the other three drugs is inconstant and uncertain, when amounts are given that will not cause other systemic effects.

3. These experiments open new avenues of valuable clinical physiologic research on man.

#### DISCUSSION:

DR. M. B. DREYER (Halifax, Nova Scotia): As a pharmacologist, I have to listen to a good many heresies. I don't want to take Dr. Bargaen to task at all, but if one is going to use doses, use heroic doses. Secondly, "peristaltin," while it may be an excellent drug, should be considered from the point of view of kidney damage. Its indiscriminate use may lead to kidney damage.

I am more particularly interested in the use of pituitrin. The effect of it varies with the portion of the gastro-intestinal tract selected. The colon is particularly sensitive

to small doses, in that small doses of pituitrin (and I am speaking of the effects on cats) showed two effects: increase in tonus and increase in number of contractions per minute. All doses as I have used them were given intravenously.

Now, in the small intestine, strange as it may seem, in the cat and the dog (these results have been confirmed by Grüber), pituitrin causes relaxation of the small intestine. The effect of pituitrin varies on the pylorus and cardiac portions of the stomach. In the pylorus, pituitrin causes strong contractions, and at the cardia it causes a relaxation. To show that it is a real effect, one can compare that with the effect of histamine in the gastro-intestinal tract, where the histamine has a stimulating action on the colon but causes relaxation of the small intestine. Like pituitrin, it is followed by a period of increased activity. There is a well known tolerance produced by pituitrin, but it is less marked for the colon and most marked for the pylorus.

If one repeats the injections of pituitrin too rapidly, the pylorus will not respond and the large intestine will. That is similar in many respects to the effect of pituitrin on the uterus. The uterus is the organ in the body most tolerant to the action of pituitrin.

The fraction of pituitrin responsible for these motor effects on the intestine is "pitressin," and not "petressin" as such, but the interesting point is this, if you increase your dose of "pitocin," because it is 96 per cent pure, as you increase that, you eventually find that the large intestine will respond to pitocin but the small intestine will not respond at all.

Perhaps one should say there is some difference in the large intestine as compared with the small, which will make it respond to pitressin.

Another thing about the large intestine which might be considered is that it is an extremely sensitive portion of the intestine and its mucosa is considerably more sensitive to purgatives than is that of the small intestine, as shown by the recent work of Straub. He found that infusion of senna (10 per cent) will cause increased movements in the small intestine, whereas 0.1 per cent of infusion of senna will cause marked movement in the large intestine and will be ineffective on the small intestine.

Another point which perhaps might be stressed is this: Dr. Barger said that bismuth is absorbed from the large intestine. Now, as a student, each of us was probably taught if there is one thing in which the large intestine differs from the small, it is that it acts as an excretory organ, and if you take bismuth and give it, you will get a blackening of the mucosa. One doesn't deny it might be absorbed from the large intestine.

Now, to utter one violent heresy, the large intestine, as you know, has three longitudinal bands and a lot of circular muscles. If you look at the large intestine when you produce a peristaltic wave, you find that the peristaltic wave confines itself almost exclusively to the circular coat and that the longitudinal bands are there merely for support of the circular coat; and, secondly, produce retraction to allow the circular muscle in contracting to pass the movements on better.

I should like to ask Dr. Barger to observe when he gives morphine to a human being, say with the barium, in the large intestine, whether there are any increased reversed peristaltic waves following the use of morphine and some of the other drugs he uses.

DR. WALTER A. BASTEDO (New York, N. Y.): We like to see experiments such as these made on the human animal because, in the last analysis, that is our guide for the use of drugs in medicine. I have done animal experiments on the bowel with some of these drugs, particularly physostigmine, but also with pituitrin and atropine.

As to the four drugs mentioned, we have to think of pituitrin as acting on the muscle essentially. That puts it in quite a different category. Physostigmine, or eserine, acts essentially by enhancing and prolonging the influence of vagus stimulation. Acetylcholine has the effect of vagus stimulation if you can put it in the right place, but acetylcholine by hypo is very quickly destroyed by the tissues of the body or in the blood stream. Cascara, (represented by "peristaltin")—well, there isn't any active principle of cascara that has ever been isolated that will produce the same effect as cascara; and although you can get some action by hypodermic material made from cascara, unless one gives a great deal, much more than one would have to give by mouth, one can't get any effect on the bowels.

As far as the dose of eserine is concerned, a number of years ago I tested patients, post-operative, with physostigmine by hypo in doses of 1 milligram and two milligrams, and found it very inefficient. Sometimes we would get a little action and sometimes we wouldn't get any, even from two milligrams, that is, a thirtieth of a grain.

Martin and Weiss obtained very good results from double that dose, four milligrams, a fifteenth of a grain, but when one reaches that point of dosage, as Dr. Barger has pointed out, one begins to get the toxic symptoms of physostigmine, which, as you know, are nausea and salivation, and, very strikingly, cramps in the bowel.

We found that physostigmine tends to increase peristalsis in the small intestine and to increase the tone waves into spasm or cramp. This effect can be completely overcome by atropine. We don't want cramps, and cramps result from physostigmine in dosage just a little larger than that which tends to stimulate peristalsis.

Of course, when we talk about peristalsis in the large bowel, I don't think we know much about it. We know a lot about the small bowel because that organ is so much more easy to work with, as its actions are rapid. We must think of the large bowel as an organ that holds back material instead of pushing it on, the small bowel emptying liquid into the large bowel all day long, and the large bowel expelling solid material only once or twice a day. The colon's job is to hold things back, not to push them along, except at very rare intervals; therefore, we have to be careful not to transfer the results of experiments on the small intestine to the large.

Just one more point: Drugs that stimulate the vagus—I mean that enhance the action from vagus stimulation—depend for their action, as vagus stimulation does also, on the state of the bowel at the time. If the bowel is contracted, if it is hypertonic, stimulation of the vagus causes it to relax—again I have made a mistake—we shouldn't say "vagus," but rather parasympathetic, for the vagus does not supply the colon in man. If the colon is in a relaxed state, parasympathetic stimulation tends to cause its contraction. This apparently contrary action, according to whether the bowel is in hypertone or hypotone, is a new idea to us medical men, but a fact established by a great many experimenters at the present time.

DR. J. ARNOLD BARGER (closing the discussion): The suggestions of Professor Dreyer and Dr. Bastedo are very much appreciated. The opportunity for further intensive study of other drugs is constantly at hand. We chose the four drugs mentioned because they are the ones in common usage among surgeons and clinicians in the control of paralytic ileus of various kinds. We realize that the work of the last few years has but opened the field. We hope that these discussions will stimulate others sufficiently so that more intensive studies of this type will be undertaken.

# Some Normal Variations in the Emptying-Time of the Human Stomach (Using a Carbohydrate Meal)\*

By

EDWARD J. VAN LIERE, Ph.D., M.D.

and

CLARK K. SLEETH, A.B., B.S.

MORGANTOWN, WEST VIRGINIA

IN the course of some experimental work upon the emptying-time of the human stomach (1) considerable data pertaining to the normal emptying-time was obtained. Some rather interesting variations were noted in connection with these data, and led us to believe that this report might prove of interest to gastroenterologists and to experimental physiologists.

It is well understood that many factors may influence the rate of gastric emptying, and that even when every attempt is made to control all of these factors and to produce uniform experimental conditions, a careful evaluation of results is necessary.

## METHOD

Nine normal young adult male medical students were selected for this work. They were given a standard meal, which was prepared as follows: 15 grams of farina and 1 gram of salt were added to 350 c.c. of boiling water and the mixture was cooked until the total volume was 200 c.c. This semi-solid preparation was kept in an electric refrigerator overnight. The next morning 50 grams of barium sulphate were added, and the meal was eaten at 8:30 A. M.

After the subjects had eaten the meal they were asked to lounge about the laboratory, and for the main part to keep seated in comfortable positions. They were allowed

at about what time gastric evacuation would occur, for, as is pointed out later, the emptying-time of the stomach for each individual remained singularly constant from day to day. This method of estimation prevented undue exposure to the Roentgen ray.

## RESULTS

Nine subjects were used, and a total of 77 tests was run. The arithmetic mean (average) of the emptying time of the stomach of the 9 individuals was 2.07 hours. The arithmetic mean of the 77 tests was 2.08 hours. The extremes of the emptying time for the subjects were 1.03 and 2.81 hours, respectively. The extremes for the tests were 0.75 and 3.50 hours, respectively.

## DISCUSSION

It is interesting to observe that the emptying time of any individual varied but little from day to day. Even in such cases as subjects number 4 and 9 respectively, where there is considerable difference between the extremes, the mode and the median check closely with the average emptying time. A similar constancy has been observed in previous work upon animal subjects (2).

It must be noted that our standard meal consisted almost entirely of carbohydrate. It is doubtless true that a meal with a higher protein content would be retained longer by the stomach, since such a meal would be subjected to a certain amount of gastric digestion before it would be allowed to leave the stomach. The meal we used was chosen for ease in preparation and administration, and to conform with standards previously set up by other workers on the emptying time of the stomach (3).

It is seen that the emptying-time of the stomach of subject number 1 is considerably shorter than the average. This subject reported that when in perfectly normal health he had 2 or 3 bowel movements every day. Subjects number 8 and 9, each with a rather long emptying time, were high-strung individuals.

These points of information are not given in an attempt to explain why the emptying time in these cases varied considerably from the average, for it is certain that in a series of persons chosen at random a number of just such individuals would be encountered. We feel, therefore, that the subjects used in this work represent a fairly accurate cross section of their group.

Owing to the small number of subjects used in this work no attempt was made to correlate our objective

TABLE I

Table I gives the details of the results obtained

| Subject Number | Emptying Time in Hours |         |                       |      |        | Number of Tests |
|----------------|------------------------|---------|-----------------------|------|--------|-----------------|
|                | Shortest               | Longest | Arith. Mean (Average) | Mode | Median |                 |
| 1.             | 0.75                   | 1.50    | 1.03                  | 1.00 | 1.00   | 7.              |
| 2.             | 1.25                   | 2.00    | 1.58                  | 1.50 | 1.50   | 9.              |
| 3.             | 1.75                   | 2.25    | 1.96                  | 2.00 | 2.00   | 7.              |
| 4.             | 1.50                   | 2.50    | 2.00                  | 1.75 | 2.00   | 11.             |
| 5.             | 1.75                   | 2.50    | 2.17                  | 2.25 | 2.25   | 10.             |
| 6.             | 2.25                   | 2.25    | 2.25                  | 2.25 | 2.25   | 7.              |
| 7.             | 2.25                   | 2.75    | 2.40                  | 2.25 | 2.25   | 7.              |
| 8.             | 2.25                   | 2.75    | 2.50                  | 2.50 | 2.50   | 10.             |
| 9.             | 2.25                   | 3.50    | 2.81                  | 2.75 | 2.75   | 9.              |
| Average        |                        |         | 2.077                 |      |        | 8.5             |

to spend part of the time in reading light fiction, such as may be found in current non-scientific periodicals. In short, they were asked to relax, physically and mentally, as much as possible, without making a studied effort to do so. Every precaution was taken to shield them from extraneous influences.

The emptying-time of the stomach was determined fluoroscopically. After a few determinations had been made upon any individual it was relatively easy to estimate

\*From the Department of Physiology, West Virginia University.  
Submitted August 19, 1935.

findings with weight, physique, mental makeup, or any other characteristic.

### SUMMARY

The normal emptying time of the stomach of 9 young adult males was determined fluoroscopically, under carefully controlled conditions. The standard meal used consisted chiefly of carbohydrate; the preparation of the meal is described in the body of this paper.

A total of 77 tests was made. The arithmetic mean (average) of the emptying time of the 9 subjects was 2.07 hours. The arithmetic mean for the 77 tests was

2.08 hours. The extremes for the subjects were 1.03 and 2.81 hours respectively. The extremes for the tests were 0.75 and 3.50 hours respectively.

It was found that the emptying time of the stomach of any individual remained strikingly uniform from day to day, but that great individual variations exist.

### REFERENCES

1. Van Liere, E. J., Lough, D. H., and Sleeth, C. K.: "The Effect of Anoxemia on the Emptying Time of the Human Stomach." *In Press. Arch. Int. Med.*
2. Van Liere, E. J., Lough, D. H., and Sleeth, C. K.: "Normal Emptying Time of the Stomach of the Dog." *Proc. Soc. Exp. Biol. and Med.*, Vol. 31, pp. 85-87, 1933.
3. Hellebrandt, F. A.: *Personal Communication.*

## ABSTRACTS

RIEGL, CECILIA, RAYDIN, I. D., MORRISON, PHILIP J., AND POTTER, MILTON J.

*Studies of Gall Bladder Function. XI: The Composition of the Gall Bladder in Pregnancy. J. A. M. A., 105:1343, Oct. 26, 1935.*

Gall bladder disease follows pregnancy too often to be considered a mere coincidence. It has been thought that this results from some alteration in the bile during pregnancy. It has been shown that alterations in the chemical composition of the bile accompanies biliary tract disease and previous studies have demonstrated that damage to the gall bladder wall is accompanied by marked changes in the composition of gall bladder bile. It therefore becomes very interesting to know what the gall bladder bile removed from pregnant patients at term with no history of gall bladder disease would reveal. Data from the studies of thirty-four specimens of such bile removed from living women at term during the course of cesarean section revealed that the composition of such bile was changed from the normal. Chemical examination of this bile revealed that the cholesterol concentration is increased while the bile salt concentration is below normal. These changes in the pregnant gall bladder bile are in the direction that one would expect to precede stone formation.

Francis D. Murphy, Milwaukee.

DENNY-BROWN, D., AND ROBERTSON, A. GRAEME.

*An Investigation of the Nervous Control of Defaecation. Brain, 58, 256-310, 1935.*

The defaecatory process in healthy man and the automatic defaecation resulting from destructive lesions of the sacral cord were studied.

(1) Where the sacral innervation of the rectum and anus has been destroyed, there occurs contraction of the rectum with reciprocal relaxation of

the anal sphincter. This reciprocity is nervous in mechanism, being related solely to the peripheral (intramural) nervous plexus. The adequate stimulus for relaxation of the anal sphincter is tension upon the wall of the rectum. Changes in tension are more efficient than passive tension.

(2) In "reflex defaecation" (where the sacral portion of the spinal cord is intact and is in nervous connection with the rectum and anus) the process is that of progressive and fused rectal contractions.

(3) The automatic and reflex responses are not mediated by the hypogastric nerve (i.e., they are not under the control of the sympathetic nervous system).

(4) Voluntary control over defaecation extends only to the external voluntary sphincter ani. The external sphincter is not tonic, but it contracts synergistically with the abdominal parietes in the course of the *flexion* reflex.

(5) If delivery of faecal material to the colon is adequate, the mechanism of defaecation depends primarily upon the reaction of the rectum to distension.

M. H. F. Friedman, Montreal.

ARNOLD, J. R., BERGH, G. S., AND IVY, A. C.

*"Peptic" Ulcer and the "Anxiety Complex." S. G. and O., Vol. 61, No. 2, pp. 162-168, Aug., 1935.*

The Authors performed experiments designed to determine whether chronic peptic ulcers could be produced in the dog by:

1. A sustained stimulation of the motor activity of the stomach.
2. Maintenance of the secretory activity of the stomach at a high level.
3. Continuous motor stimulation together with a high acid level. Since even the wildest of jungle animals soon become accustomed to the unnatural conditions of captivity, and, according to those who are familiar with their

habits, show no signs of emotional stress, it was not possible to study the effect of that factor in the production of peptic ulcer.

Three groups of dogs were studied. The first group was given 2.5 milligrams per dose up to 37 days. The second group was given 2 milligram doses of histamine over periods varying from 63 to 66 days. The third group was given a mixture of pilocarpine and histamine in doses of 2 milligrams each for periods up to 58 days. Injections were given every two hours for 10 doses daily after which the dogs were given a "smooth" ground diet. Gastric analyses, throughout the 24 hour period, were made one to three times a week. At the completion of the experiments the animals were sacrificed, and careful autopsies were performed. Sections were made of the liver, kidneys, adrenals and stomach.

Most of the dogs in the first group showed no change throughout the intestinal tract except a slight injection of the duodenum in some cases. None of the dogs in the second group showed chronic ulcers in the intestinal tract at the completion of the experiment; some showed small superficial erosions. In all of the dogs in that group a high free acidity was found throughout the experiment. In one of twelve dogs in the third group a small erosion was found in the stomach. The intestinal tracts of the others were found to be normal. The liver, kidneys and adrenals were found to be normal in all dogs excepting those receiving obviously toxic doses of the drugs.

The Authors conclude that hypermotility of the stomach in combination with high acidity, as produced by pilocarpine and histamine, respectively, does not produce chronic peptic ulcers in the dog.

A large bibliography accompanies the article.

Nelson M. Percy, Chicago.

## SECTION VI—*Abdominal Surgery*

### Experiences with Postoperative Jejunal Ulcer and Gastrojejunocolic Fistula\*

By

FRANK H. LAHEY, M.D.†  
BOSTON, MASSACHUSETTS

THERE are probably no two subjects today about which there has been a wider divergence of opinion or a more diametrically opposed attitude than that of the advisability of employing subtotal gastrectomy in the surgical treatment of intractable duodenal ulcer‡ as opposed to gastro-enterostomy and the incidence of postoperative jejunal ulcer following gastro-enterostomy.

In a recent review of the literature on this subject, we found the incidence of gastrojejunal ulcer after gastro-enterostomy reported as low as 1.7 per cent (Walton) and as high as 24 per cent (Strauss, Bloch, Friedman) and after gastric resection as low as 0.4 per cent and as high as 10 per cent.

Such a wide variation in figures on the part of men with experience must of necessity be due to irregularities in methods of arriving at these conclusions such as, whether or not diagnoses of gastrojejunal ulcer were made by actual demonstration of the lesion at operation, in which case the diagnosis is established with certainty, or whether or not the diagnosis was made from symptomatology and by X-ray, in which event in at least a considerable number of cases, it has been our experience that the diagnosis must be in doubt. All of these figures represent just patients upon whom gastro-enterostomy has been done, with no attempt to separate (if it is a possible undertaking) those patients with recent ulcers from those with long-standing ulcers, the young people with high acids from the older individuals with lower acids, those patients with pyloric obstruction from those with a patent pylorus and those patients with repeated histories of bleeding and so the posterior wall eroding ulcers that are notably difficult to manage by any method of treatment. Likewise, these figures include impartially those patients who have had good postoperative dietary management with those who not only have had none but have resumed the habits of life which played a considerable part in the production of the ulcer.

The figures for recurrent ulcer following subtotal gastrectomy represent a massed group of postoperative results in which no segregated data is available as to whether the resection was a radical one calculated to be followed by a low gastric acidity or anacidity,

or what amounts to a pylorotomy, probably to be followed by a higher gastric acidity.

With the above stated variables present, it is only possible to arrive at what amounts to approximate conclusions concerning the incidence of this lesion; but as more and more time passes after the era during which there was an unreserved enthusiasm for gastro-enterostomy as a method of treating gastro-enterostomy, it becomes more and more evident to us that while one cannot state in accurate figures the percentage incidence of gastrojejunal ulcer after gastro-enterostomy, nevertheless so many patients are presenting themselves at our Clinic with this lesion, together with the accumulating data, (see particularly the recent report of seventy-nine carefully followed cases by Hinton with 16 per cent gastrojejunal ulcer, six by operation and seven by careful X-ray study) and the depressing experiences of Graham with forty-three carefully followed postoperative cases, that we are convinced that gastro-enterostomy is not a justifiable routine operation in the surgical treatment of duodenal ulcer. We are further forced to this conviction by our operative experiences with this condition.

We have operated upon thirty cases of gastrojejunal ulcer and gastrojejunocolic fistula with a mortality of 15 per cent. This mortality rate represents approximately the average mortality rate for this condition. With an increasing background of experience, this rate can perhaps be lowered somewhat but when one deals with a lesion as complicated as this one is, high in the upper abdomen where the risk of surgery is great, in patients often in poor condition, requiring complicated technical procedures that consume long periods of operating time and which are known to be followed by a high percentage of pulmonary complications, there will always be here, I believe, a disturbing mortality rate.

Of the thirty cases, ten had excision of the gastro-enterostomy together with the ulcer, anastomosis of the jejunum and reestablishment of the alimentary tract to its normal course, that is, without subtotal gastrectomy. In all of these cases, the original duodenal ulcer was found to be healed but following the excision of the jejunal ulcer and the gastro-enterostomy, either the original duodenal ulcer has been reactivated or a new one has developed in 40 per cent of the cases.

\*Presented at the 38th Annual Session of the American Gastroenterological Association, Atlantic City, N. J., June 10-11, 1935.

†Approved by the Publications' Committee of the Association.

‡Lahey Clinic, Boston.

§There is little or no conflict of opinion regarding subtotal gastrectomy for intractable gastric ulcer.

From this experience, together with that of Graham who reports that in three cases in which the gastro-enterostomy was taken down, the gastrojejunal ulcer removed and the stomach restored to its original state, all are now suffering severely from duodenal ulcer symptoms, it seems to us that this is not a satisfactory surgical procedure for the treatment of gastrojejunal ulcers. He also reports that in twenty-eight cases with pyloroplasty for duodenal ulcers, postoperative X-ray studies showed constant hypermotility and no brilliant surgical cures.

We have had eight cases of gastrojejunal ulcer proven by X-ray and histories that have been conditionally treated medically. Three are well, six, eight and twelve months after first being seen. One has gone four years but has had severe ulcer symptoms fairly controllable by treatment. One has been under observation but six months and is unable to work, one died of perforation two years after the beginning of his treatment, two are free from symptoms but have had hemorrhages, one two years after treatment and one four years after treatment.

While the outlook for medical treatment of gastrojejunal ulcer is far from satisfactory, it must be admitted that contrary to what used to be our opinion, it is possible to carry some patients with gastrojejunal ulcer along with fair satisfaction under non-operative forms of treatment.

It is of interest to know that in none of our demonstrated lesions was the gastrojejunal ulcer truly gastric, being jejunal but marginal in location in 75 per cent of our cases and completely jejunal in 25 per cent.

Starlinger reported from the literature, one hundred and fifty cases of perforation in gastrojejunal ulcer. On the basis of twenty-five hundred cases estimated by him to be in the literature, he considered the percentage of perforation after gastro-enterostomy as 5.6 per cent and after resection 3.3 per cent. The percentage of perforation in our series was 9 per cent and the percentage of hemorrhage in our series 13 per cent as opposed to 18 per cent in our patients with duodenal ulcer.

When one considers the causative factors of gastrojejunal ulcer, one must, I believe, consider hyperchlorhydria as the factor occupying a position of first importance. Gastro-enterologists are so acutely aware of the relationship of increased gastric acids to ulcer and particularly gastrojejunal ulcer that I do not need to do more than mention some of the evidences of its quite constant linkage with this lesion.

Gastrojejunal ulcer is rare in women who have lower acids than do men.

It almost never occurs in gastro-enterostomy for carcinoma of the stomach.

In our series of gastrojejunal ulcers, the lesion followed gastro-enterostomy for duodenal ulcer in 90 per cent of cases and for gastric ulcers in 10 per cent. This is quite suggestive in view of the high acids in duodenal ulcer and the lower acids in gastric ulcer.

Of further significance is the so often proven fact that the lower down the jejunum one places these anastomoses to the stomach and so the farther away from the segment which has adapted itself to receive acids, the easier it is to produce experimental ulcers.

until they can be quite regularly produced in anastomoses made to the ileum.

Surgical technique has often been reproached as a causative factor in gastrojejunal ulcer but in my opinion has little if actually anything to do with it and I will set down a few reasons why I believe this to be true.

It used to be said that the employment of silk or linen in the suture line of the anastomosis between the stomach and the duodenum because it acted as a foreign body, was the cause of these ulcers and this position was strengthened by the fact that strands of silk would be found hanging in the beds of those ulcers where erosion had taken place about the foreign body. Because of this feeling, all non-absorbable suture material has now for several years been given up and only catgut used by almost all surgeons and yet the percentage of gastrojejunal ulcer remains just as high. As has been said the silk or linen is not the true offender but just an innocent bystander.

It used to be said that gastrojejunal ulcers were caused by too tight gastro-enterostomy clamps but just as many ulcers now follow gastro-enterostomy done without clamps.

It used to be said that these postoperative ulcers followed operative trauma to the suture line, but the entire question of the relationship of operative trauma to gastrojejunal ulcer is largely eliminated by the fact that gastrojejunal ulcers occur fifteen to twenty years after gastro-enterostomies and so are quite definitely unassociated with any question of relationship to operative technique.

In a group of fifty cases of gastrojejunal ulcer taken at random, the average time of recurrence was two years and cases of gastrojejunal ulcer have been reported as occurring from a few weeks after gastro-enterostomy up to twenty-one years. The longer a patient with a gastro-enterostomy for peptic ulcer goes without a gastrojejunal ulcer, the less likely he is to have one. Nevertheless, the occasional development of such a lesion years after operation indicates that he is never free from the possibility of the occurrence of such a lesion.

There are certain signs and symptoms in patients who have had gastro-enterostomy for peptic ulcer which point strongly toward the diagnosis of this condition. If a patient has had duodenal ulcer and the symptoms have been relieved by a gastro-enterostomy and then recur and with greater intensity, one must be extremely suspicious that the symptoms are due to the occurrence of a gastrojejunal ulcer. As the result of our experience with these conditions, we are impressed with the fact that in practically every case in which we have had the opportunity to observe the original duodenal ulcer after gastro-enterostomy, it has been found to have healed. We are of the opinion as the result of these observations that it is very much more common for a gastrojejunal ulcer to occur following a gastro-enterostomy than it is for the old duodenal ulcer to be reactivated. If the original point of tenderness in the right upper quadrant following the recurrence of ulcer symptoms in the presence of a gastro-enterostomy shifts to the left of the umbilicus over the gastro-enterostomy stoma, it is strongly suggestive that this tenderness is the result of a gastrojejunal ulcer.



Symptoms of perforation in a patient who has had a gastro-enterostomy should make one extremely suspicious that the perforation is of a gastrojejunal ulcer and not the original duodenal ulcer. When a gastro-enterostomy has been functioning and then ceases to function and closes, one should be suspicious that this closure is the result of the inflammatory reaction associated with a gastrojejunal ulcer.

Hemorrhage late after gastro-enterostomy while less suggestive than some of the above mentioned factors, must nevertheless be considered distinctly a possible indication of the presence of a gastrojejunal ulcer.

While I have often employed the Hibernianism regarding the prevention of gastrojejunal ulcer, that the best prophylaxis against gastrojejunal ulcer is not to do a gastro-enterostomy, nevertheless, gastro-enterostomy must occasionally be employed, in which case the only prophylaxis is the realization by the patient of the real likelihood of his having such an ulcer, the real seriousness of such a lesion if he has it and the need for the rest of his life to modify his living, eating, smoking and drinking habits.

There are certain features about gastrojejunal ulcer which are quite universally accepted. The lesion is undoubtedly very apt to occur in young people, with duodenal ulcer, who have high gastric acids. Its incidence is increased if in addition to a gastro-enterostomy, the pylorus is occluded, thus preventing the return of alkaline duodenal contents into the stomach. It is likewise more apt to occur after a gastro-enterostomy if enterostomy is done between the two loops of the jejunum, thus sidetracking the alkaline jejunal contents and preventing their return into the stomach through the gastro-enterostomy stoma. While anterior gastro-enterostomy must be made with a long loop of jejunum up over the transverse colon, and so at a lower jejunal level more susceptible to ulcer, there are no really convincing figures to prove that this is so. Unconventional as the position may be, I must as the result of my experience with the gastrojejunal ulcer state that if I had to have a gastro-enterostomy for duodenal ulcer, I believe that I would feel safer with an anterior one than with a posterior one. I take this position because I feel sure that the surgical management of a gastrojejunal ulcer in an anterior gastro-enterostomy is safer and easier than it is in a posterior gastro-enterostomy.

As the result of our experience, I am more and more convinced that the best operation for gastrojejunal ulcer is the one which results in the lowest percentages of gastric acid postoperatively and that undoubtedly is subtotal gastrectomy.

While it is my conviction that many skeptics (and I have been one) will with increasing experience have, as have I, the above conviction forced upon them, still the problem remains an extremely serious one. The operation is a very difficult one technically. Familiarity and facility with its performance requires a considerable experience with it and even in spite of this, my own mortality is far from a comforting one. Patients who are candidates for such serious operations are often in poor condition, the operation is necessarily long and postoperative complications are inevitably associated with it. In spite of these non-reassuring observations, progress may still be accomplished in these patients. In another paper on this subject, I stated that I was a little disturbed to make the follow-

ing statement but the oftener I make it, the less self-conscious I am about it.

We must make clear to all patients, particularly with duodenal ulcer, that indirect operative procedures which have a relatively low mortality rate, are followed by a relatively high percentage of postoperative ulcers, that these ulcers are intractable to non-operative measures and have associated with them a relatively high mortality rate in their satisfactory surgical treatment; that the surgical operation which is followed by good results and a low percentage of recurrent ulcers has a relatively high mortality rate and that with the above in mind, doctors must advise and patients must adhere to an extremely strict non-operative ulcer regime. If this is done, and surgery becomes necessary, then the lesion simulates that of malignancy and the risk becomes unquestionably justifiable. If the regime is advised and adequate, but is not pursued, then the responsibility places itself squarely where it belongs. If on the other hand, patients are permitted to believe that peptic ulcers are not serious lesions, that the surgical treatment of this condition is quite satisfactory and that permanent changes in eating, drinking, smoking and living habits are not necessary, then the ultimate responsibility for the unhappy situations which are bound to arise in patients with ulcer will be largely upon the shoulders of the medical adviser.

#### DISCUSSION:

DR. L. J. AUSTIN (Kingston, Ont.): The last two papers combined must indeed make us feel extraordinarily unhappy. We are between the Scylla and Charybdis of obesity and dyspepsia, and, as far as we can see, the obesity has the advantage. There are some tremendous advantages in being enpeptic; I am.

We heard last night at dinner a discussion of the history, of the technique, of gastro-enterostomy, its variations, the different sorts of sutures, the dangerous, and some of the immediate rather than the remote sequelae of these operations, and I suppose there isn't a surgeon of today, even in a big clinic, who doesn't sometimes, occasionally hit up against an obstruction case, or, if you prefer to call it a vicious circle; and there is no question that gastro-enterostomy gives us furiously to think.

Now, when I was a student, I served my time under some of the pioneers of gastric surgery in London, Mr. Mansell-Moullin, who did not write much about it, Mr. James Sherren, who certainly was a pioneer in gastric surgery in England, and also under Mr. Albert J. Walton, who was only a few years senior to myself but had the good fortune to be on the staff while I was still an intern—there is a great deal of difference in that, you know—and he certainly was a beautiful technician, and is still a beautiful technician; and during the time in which I was a sort of junior staff man, what we called "registrars," I made a fairly intensive study of those cases operated on by my chiefs, and they didn't all come out quite so successfully as I had hoped.

You will remember when the plain gastro-enterostomy was introduced, it was thought to be a panacea for all stomach troubles—a little weeping hemorrhage, gastritis following several days of, you know, the night before, and for the relief of all forms of gastric and of duodenal ulcer; but, as Dr. Lahey has shown us today, surgeons and physicians have gradually come to the conclusion that that is a very mistaken idea, that gastro-enterostomy has but a limited application.

The first change I noticed was that it began to filter into the minds of some people that gastro-enterostomy, a plain gastro-enterostomy, would not be very successful

unless it was a degree of obstruction, and I think it was from some of the very successful cases of obstructed pylorus due to ulceration, and to the great relief obtained in many of the cases of carcinoma with obstruction, that the blocking of the pylorus was adopted, in a measure to make an artificial obstruction so as to insist upon the sterner work.

The technical difficulties of doing a gastro-enterostomy are not really, I think, to be lightly thought upon, and no surgeons who are growing up in any school should be allowed to dash off and do gastro-enterostomies, alone and by themselves without a certain amount of training. There is a danger of men, what you might call "gnawing up" patients, without adequate training. We all know that happens, and the attempt in the old lands, as you probably all know, is to build a specialized class of privileged surgeons, those who have the fellowship. I don't say that because a man has a Fellowship of the Royal College of Surgeons, he is naturally a God-given operator; he isn't, by a long ways, but it does mean that at one time in his life he knew his anatomy—I don't say he does now, but he did once. And even that is an advantage. It is because of the difficulty of standardization and of specialization, that both your medical association and our own Canadian association are very much troubled about this question of specialists, and we cannot expect the law to help us.

I have struggled myself very hard to find out what are the legal privileges of a doctor in the Province of Ontario. I can't find it out, but I know they are very restricted in the old land. When we were qualified in the College of Surgeons with a degree of Member of the Royal College of Surgeons and Licentiate of the Royal College of Physicians, an ordinary, qualifying, examination, we were taken into a big room, and there was a throne in it, and the President of the Royal College of Surgeons was there in his robes, and the Board of Examiners on each side of him, and after a very few remarks not lasting more than half a minute, congratulating the boys on having got through, he said, "The Secretary will now read to you the legal privileges of a medical man."

Then the Secretary got up and said, "The legal privileges of a medical man in England are four:

(1) "You can sue for your fees in a court of law."

(You all know what happens if you do that!)

(2) "You cannot be called to serve upon a jury." And that certainly applies. We can't be called to serve upon a jury.

(3) "You are not liable to the militia ballot"—and when the Great War came on, we were conscripted with the rest.

(4) And this doesn't apply nowadays very much—"Your horse cannot be taken for a fire engine."

I had the permission of the Chairman to wander a little off the subject, and I wandered off deliberately because I have not had—and it is no good saying I have—enough cases to add to the statistical importance of Dr. Lahey's report. All I know is that the cases of fistula that I have had to deal with, are, I think, most of them, happily buried now, and there is no question that it is our bounden duty, I think, to see that our patients with duodenal ulcer have the really finest medical treatment possible before they are submitted to surgery.

Sometimes you can cure them, as our President does, with tubes, and then has one done on himself. Sometimes you can suffer and then finally decide to have tubes. But I think we must admit that medical treatment is the logical and reasonable thing to try, that gastro-enterostomy, applicable as it is in some cases, is more or less an adventure and carries with it certain grave and serious risks.

To say I am happy about doing gastro-enterostomy is absurd, and I think that my attitude towards the whole

matter might be summed up in the few words of Cardinal Woolsey, in Shakespeare's "Henry VIII":

"I have ventured,

Like little wanton boys that swim on bladders,

This many summers in a sea of glory,

But far beyond my depth."

DR. PAUL W. ASCHNER (New York, N. Y.): It is with some sense of gratification that we hear Dr. Lahey express himself today as he did, as unwilling and unhappy when he has to do a gastro-enterostomy for duodenal ulcer.

Now it would be almost presumptuous to go into a discussion of the underlying fundamental cause of jejunal ulcer when we do not know the underlying fundamental cause of duodenal ulcer; however, there are certain factors that we do know from experience and study. One is that there is such a thing as gastritis and duodenitis; that it is in all likelihood the predecessor of ulcer and that even after we have attacked the ulcer surgically, it is quite possible for that process to go on in the remaining portion of the stomach which we leave behind when we have done a subtotal resection, or which we certainly leave behind when we do a gastro-enterostomy, and that, moreover, the same process may appear in the jejunum.

We also know from some of our studies that the disease of gastritis and duodenitis is one which has a tendency to undergo, in the course of time, a recession with diminution of the activity of the glands of the stomach, and lowering of the acidity. The cases possibly favorable for gastro-enterostomy are those which have a low acidity, and in which the obstruction of the pylorus is not due to an acute inflammatory edema about an active ulcer, but in which there has actually been such a recession of the disease that scar formation and cicatrization have taken place. In these cases we are no longer dealing with ulcer and ulcer disease, but rather a mechanical obstruction.

There is one thing of interest in this connection I want to point out. Jejunal ulcer does not occur when a gastro-enterostomy has been performed in a patient who did not have a duodenal ulcer, or a gastric ulcer to begin with; in other words, it is the underlying disease which predisposes.

The dangers of the secondary operation when jejunal ulcer has occurred—and I might say by the way, Dr. Lahey, that in our experience we find jejunal ulcer, much more common than marginal, and frequently multiple—the dangers are many, in the technique of operating these cases.

As to the mortality to be arrived at in secondary resections, Dr. Lahey once made a very fine suggestion. I don't know whether he is still following it. It was to divide this operation into two stages, to take down the gastro-enterostomy closing both sides as one stage, and at a second stage to do the resection of the stomach to prevent the patient's getting the duodenal ulcer he is certain to get if resection is not carried out.

DR. B. B. VINCENT LYON (Philadelphia, Pa.): The Chair would ask permission to make the following remarks:

You have noticed that in this year's program, we purposely dodged the acceptance of all papers dealing with peptic ulcer, gall bladder disease, and, to some extent, colitis, because of the continued confusion in properly handling the discussion of such topics.

I should like to point out, as all of you who go back thirty or thirty-five years will remember, that we were taught that peptic ulcer could be cured surgically by gastro-enterostomy alone, or medically by the Sippy method or other medical regimes. You have seen for yourselves what has happened in regard to this subject over that twenty-five, thirty, or thirty-five years.

This problem, gentlemen, is today just as unsolved as it was when we were given the answers to it in that day. I speak of this to point out to you the need of what I suggested yesterday, a national research institute devoted

solely to the solving of gastro-intestinal problems, by which scattered views can be assembled and a concentrated attack made on one common problem chosen in a proper way.

DR. FRANK H. LAHEY (closing the discussion): I appreciate that this subject of ulcer is a trite one. At any meeting, it always occasions a great deal of discussion. I appreciate also the muddle in which the entire peptic ulcer situation is, and I particularly appreciate how difficult it would be for anyone who has a duodenal ulcer after listening to this discussion, to arrive at some definite plan of approach.

I was very much interested to hear Dr. Lyon's personal experiences with gastro-enterostomy. It is nice of him to be willing to state them.

When Dr. Aschner discussed my paper, I presumed I was in a group of medical men, and so I asked Alfred Strauss if Dr. Aschner was a surgeon, and he said, no, he was a medical man which turns out not to be true. I was about to tell the story, if he had happened to be a medical man, about a colored man named Jake who worked for me in the South, where for several years I have had a shooting place.

One day a colored hobo arrived at the plantation via freight train and he was a type not uncommon in the South with long, thin legs, with no muscles, all bone, and in our part of the South that type is called a "shinbone nigger." He was sitting on the porch of the little country grocery store on a box, with his pantaloons pulled up, and his bare, thin shinbones sticking out, and Jake, sitting beside him in the sun, leaned over and looked at his legs and said, "Dave, has you ever had de dropsy?"

And Dave said, "No, Jake, I ain't never had de dropsy. What for does you ask me has I had the dropsy?"

And Jake said, "Well, I was going to say, has you ever had the dropsy, you're the cured-est nigger of it I is ever seed."

I was about to say if Dr. Aschner was a medical man, he is the surgical-est medical man I have seen.

Now, while I do not want to discuss surgical technique, there is one thing I would like to say: I would urge those of you who watch gastro-enterostomies, if they are ever done, to beg the surgeon to do a reasonably long loop gastro-enterostomy and he will thus make it easier for the next surgeon when he deals with a gastrojejunal ulcer.

I know of nothing which has caused me greater distress and which has resulted in more mortality than having to operate upon patients with gastrojejunal ulcer who have had a no loop gastro-enterostomy. This has compelled me

to do an end to end anastomosis on a jejunum with only a half an inch of that structure intraperitoneal.

As to subtotal gastrectomy, I make this as an admission, because I was an opponent of subtotal gastrectomy, I think all of us should frankly admit that we owe to Finsterer, Harberer, Strauss, Berg and others a debt of gratitude for adhering in the face of criticism to the position that subtotal gastrectomy is the best operation for patients with intractable peptic ulcer. It is true that we have assessed gastro-enterostomy after thirty years and, to be fair, we must likewise assess subtotal gastrectomy after thirty years, but at the present time, we surgeons who receive these patients from you when you have exhausted non-operative measures, must take a position; subtotal gastrectomy, as one acquires the technique of the operation, is, I am convinced a better operation than is gastro-enterostomy.

Sometimes my surgical friends say, "I don't have jejunal ulcers." That is wrong. The reason is that they do not have personal follow ups. Until you get a personal follow up by someone not interested in what the incidence is, and who is critical about the end results and who does accurate studies, you do not find out what your incidence of gastro-jejunal ulcer is.

There is one criticism of the medical man I should like to make and it is a mild one. We all hesitate to admit defects even in methods of treatment. I do not believe that the poor patient really gets a fair deal when you help him make the decision about what he will do with his ulcer unless you frankly tell him that medical treatment and surgical treatment are far from what we would like them to be, I mean in the terms of high percentages of cures and non-recurrences. About everyone at the end of five years today admits around 50 per cent good results, in the medical and surgical treatment with ulcer, excepting the patients with subtotal gastrectomies.

I think if you do not say to these patients, "Medical treatment is far from satisfactory and surgical treatment likewise," how can he ever take his responsibility as to the non-operative treatment of his ulcer seriously? Certainly he approaches the subject today from the point of view that it is not a serious lesion. The man with a duodenal ulcer takes it very lightly. He even takes his hemorrhages lightly and that is wrong. If he is going to die from these lesions as a result of perforation or hemorrhage, and he is, or as a result of jejunal ulcer or subtotal gastrectomy, and he is, then the just thing to do is to impress upon him first the seriousness of peptic ulcer, and the need for accurate medical management of his ulcer. If he then does not adhere to his regime, the responsibility for recurrence or a fatality is his.

## ABSTRACTS

*Cholecystectomy in the Absence of Stone. Editorial from Lancet, 227, p. 1112, Nov. 17, 1934.*

Cholecystectomy in the absence of calculus or severe infection is no longer a dangerous operation. Hence the question raised is not the mortality of the operation but the benefit to the patient.

In Mackey's analysis of 149 cases of cholecystectomy for disease of the gall bladder without calculus 44 were cured and 44 were improved. Cholecystography was shown to be of value in predicting the success of the operation only when it showed deformity. Where the patients had suffered from attacks

of colic the operation was of value as 76 per cent were improved. Cases suffering from gall bladder dyspepsia (flatulent dyspepsia, food selection, and constipation) were disappointing and Mackey doubts whether it is justifiable to refer such symptoms to the gall bladder. Where there is no gross lesion such as catarrhal or fibrinous inflammation cholecystectomy gave relief in only 11 out of 57 cases.

In cholesterosis where the "strawberry" gall bladder (*i.e.* the mucosa covered with deposits of cholesterol) is found, it has been argued that removal is justifiable on account of impaired

absorption. However, it has been shown that tying the cystic duct does not prevent the deposit of cholesterol on the inflamed mucosa of the gall bladder in rabbits on a high cholesterol diet, hence the fallacy in such reasoning. In conclusion Mackey sums up the situation by saying that cases with well defined symptoms are likely to do better after the operation than those in whom the symptoms are vague, and, similarly, the removal of a definitely pathological gall bladder is generally more productive of gratifying results than is the removal of a gall bladder in which the microscopic appearance is equivocal.

John T. Day, Montreal.

## SECTION VII—*Surgery of the Lower Colon and Rectum*

### Traumas Resulting from Sigmoid Manipulation \*

By

BURRILL B. CROHN, M.D.

and

BERNARD D. ROSENAK, M.D.†

NEW YORK, NEW YORK

**P**ERFORATING wounds of the rectum and pelvic colon occur either in association with penetrating or crushing wounds of the abdominal wall or through the purposeful or accidental introduction of instruments or foreign bodies through the anus. Wounds of the first type include traffic and industrial injuries as well as gunshot and stab wounds. This type of injury has been amply covered in the surgical literature.

Our interest at present lies in the second type of injury; that is, those produced by the insertion of an instrument or a foreign body into the rectum. These injuries are of importance, not because of their frequency in civilian life, but because of the professional usage (for diagnostic and therapeutic purposes) of introducing various instruments into the rectum and sigmoid. The possibility of injuring the rectum and colon in the course of such procedure has been widely rumored; hitherto no compilation of data on this subject has been available in the American literature. This type of accident does not cause the majority of cases of traumatic rupture of the intestines, as was shown by Cooke (1), who reviewed seven hundred odd cases of penetrating wounds of the intestine, practically all of which were due to crushing and penetrating wounds of the abdominal wall and perineum. Accidents due to therapeutic and diagnostic procedures do constitute an important minor portion of such injuries which have never received recognition or proper emphasis; a frank and open admission of such facts should lead to an appreciable reduction of the incidence of this lamentable mishap.

Amongst civilian injuries which may cause perforation of the colon are impalements, insertion of foreign bodies into the rectum, and pneumatic injuries.

*Impalements* are accidents in which the body falls vertically upon a sharp or pointed object, driving it into the rectum. These accidents are seen not infrequently in civilian life, occurring commonly among children. They are associated in most instances with considerable injury to the external parts as well as with laceration and perforation of the colon. Rum- baugh reviewed 147 cases of impalement injuries of

the rectum and colon. Of this number 44 were treated by laparotomy and 29 or 66% recovered. Of the remaining 102 unoperated cases, 43 or 41.7% recovered.

One not infrequently hears of serious lesions, often perforations of the colon, produced by the *insertion of foreign bodies* into the rectum. The variety of objects which have been introduced into the rectum is astounding. Bottles, broomsticks, projecting knobs of furniture, hardware appliances and many other devices may be found in the rectum under varying circumstances. The commonest occurrence of this accident is in instances of ano-croticism, although it has occurred in cases of criminal assault and occasionally in so-called "pranks." The practice is doubtless widespread; the reported cases of serious traumatization are probably small in proportion to their actual incidence.

A not very frequent, but always well publicised accident is the pneumatic or air-hose injury of the rectum and sigmoid. Andrews (4), in 1911, reported 13 such injuries and many more have since been published. Some authors have attempted to determine the amount of air pressure required to perforate the colon. It will be shown later that this pressure need be no greater than that produced by a hand bulb. However, injuries produced by hose lines carrying air under great pressure are always more severe, the perforations being nearly always multiple, occurring for the most part, in the pelvic colon. The 13 cases reported by Andrews (4) were all fatalities. Since then many such cases have been saved by prompt surgery. Our own experience is limited to one case, an individual who, 5 years previously, by the mischievous insertion of an air-hose into his rectum, had suffered multiple perforations of his pelvic colon. At that time the injuries had been minimized by the physician called in the emergency and castor oil was freely administered; notwithstanding which, a laparotomy the succeeding day resulted in a protracted convalescence and eventually a complete restoration of function.

The force exerted on the bowel wall is always in excess of that required to penetrate it and the perforations are frequently multiple. Such perforations occur in the majority of instances at or about the recto-sigmoid angle because this point is more or less fixed

\*Presented at the 35th Annual Session of the American Gastro-enterological Association, Atlantic City, N. J., June 10-11, 1935.

Approved by the Publications Committee of the Association.

†From the Gastro-Intestinal Group of the Medical Services, Mt. Sinai Hospital, New York, N. Y.

and because the colon here becomes an intraperitoneal organ. Lesions which diminish the mobility of the sigmoid, such as post-operative adhesions and localized peri-colonic inflammations have been regarded as contributing elements in the etiology of some cases of perforation.

#### INJURIES DUE TO DIAGNOSTIC AND THERAPEUTIC PROCEDURES

Professor Ad. Schmidt (5), of Munich, has said "One hears much of the skill and the ability of the physician and surgeon, but much less is heard or read of the misfortunes and accidents which occur in medicine and surgery, but from these we may often learn more." With this thought in mind we have attempted to determine, the approximate frequency with which injuries and perforations occur in the course of diagnostic and therapeutic manipulations within the rectum and pelvic colon; to learn, if possible, what factors in their execution are associated with threats of danger and what possible errors of technic may lead to the incidence of such injuries. The American literature contains very few references to perforations of the colon in the course of sigmoidoscopy, there being no instance of such a report by a man who himself was responsible for the accident. French and German physicians have been more frank and have freely discussed what technical errors to avoid in order to minimize the hazards of this procedure. They have also taught the means of early recognition of technical perforations of the sigmoid and have emphasized the prompt steps necessary to meet the situation when it occurs.

A general survey of the literature has been undertaken in order to emphasize the possibility of this trauma occurring at times in the hands of those best qualified to perform such examinations.

There have been 33 cases of instrumental perforation collected from the world literature. Of these, 18 occurred in the course of proctoscopy or sigmoidoscopy; several were due to dilatation of rectal strictures, others due to the introduction of enema tips and one to fulguration of polyps. Most of the sigmoidoscopies were done by physicians; some by qualified experts, others by inexperienced general practitioners or assistants, and others were done by irregular practitioners of little experience. Anyone who does sigmoidoscopies may perforate the bowel. However, relatively few of the cases reviewed were done by experts and these were for the most part in patients who had diseased colons. Proper training under the guidance of one qualified in this field, and considerable personal experience are essential to make one a safe sigmoidoscopist. It is not true that every medical graduate is qualified to do this work or that owning a sigmoidoscope makes one a sigmoidoscopist.

In addition to a survey of the literature direct contact by questionnaire was made with 27 recognized proctologists and gastro-enterologists in the United States. A total of 21 perforations due to sigmoidoscopy were reported by this group. Of this number 5 were actually done by these specialists, 7 by assistants, and 5 perforations were seen in consultations. No data was submitted in the 4 remaining cases, except the bare recital of the occurrence. In most of the cases, the colonic wall had been weakened by the existence of carcinoma, ulcerative colitis, or diverticuli-

tis. In one of the cases reported by questionnaire and followed, the perforation was due to the fulguration of a polyp.

In addition, one of us, (B. B. C.) has had personal experience with two perforations and has indirect

TABLE I

|    |                                                      |                     |                  |                     |
|----|------------------------------------------------------|---------------------|------------------|---------------------|
| A. | <i>Reported perforations due to instrumentation:</i> |                     |                  |                     |
|    |                                                      |                     |                  | <i>No. of cases</i> |
|    | 28 American proctologists and gastro-enterologists   |                     |                  | 25                  |
|    | World literature                                     |                     |                  | 33                  |
|    | Total                                                |                     |                  | 58                  |
| B. | <i>30 Cases Reported in Detail as to Treatment:</i>  |                     |                  |                     |
| 1. | <i>No. of cases</i>                                  | <i>Recovered</i>    | <i>Deceased</i>  | <i>Mortality</i>    |
|    | 24 operated                                          | 12                  | 12               | 50%                 |
| 2. | <i>No. of cases</i>                                  | <i>Recovered</i>    | <i>Deceased</i>  | <i>Mortality</i>    |
|    | 6 unoperated                                         | 2                   | 4                | 66.6%               |
| C. | <i>Time of Operative Intervention:</i>               |                     |                  |                     |
| 1. | Up to 7 hours after perforation:                     | <i>No. of cases</i> | <i>Recovered</i> | <i>Deceased</i>     |
|    |                                                      | 13                  | 7                | 6                   |
|    |                                                      | Mortality 47%       |                  |                     |
| 2. | 7 hours to 72 hours after perforation:               | <i>No. of cases</i> | <i>Recovered</i> | <i>Deceased</i>     |
|    |                                                      | 5                   | 0                | 5                   |
|    |                                                      | Mortality 100%      |                  |                     |

knowledge of two more. The first instance occurred in the course of a routine sigmoidoscopy in which there was no disease of the colon; the patient was co-operative, the sigmoidoscopy was performed with ease and without strain. The perforation occurred while using no undue force. The other instance occurred during the fulguration of a polyp. In this last case the perforation was not at first recognized, so that several enemata had been administered before the true situation was appreciated; free air under the diaphragm and a localized peritonitis removed any doubt as to the occurrence of the trauma. Both patients recovered.

The answers to the questionnaire indicate that perforation occurs more easily in the presence of a diseased colon. This is not uniformly true, many men having seen perforations in the presence of a perfectly normal colon. It is true that the amount of force or air pressure required to rupture a thinned-out, weakened or ulcerated bowel wall is much less than that necessary to rupture the normal bowel. However, numerous cases in the literature and personal experience in one case, (B. B. C.) are convincing that no great amount of force need be exerted to push the end of the sigmoidoscope through the colon, at or above the fixed point at the recto-sigmoid angle. A case quoted by Dick (6) illustrates the ease with which a manual perforation may occur.

The greatest number of perforations reported by qualified sigmoidoscopists have occurred with the use of air inflation apparatus. The use of a hand bulb, though helpful, has not been entirely safe. Originally condemned by French authors, it is now generally considered dangerous.

The importance of passing the sigmoidoscope under direct vision has been emphasized by Buie (7) and other writers. They have cautioned that the obturator of the instrument be removed as soon as the anus is passed; the progress of the instrument must be guided entirely by the eye. Failure to observe this funda-



mental rule, has without doubt, caused many perforations.

The need for a sound knowledge of the anatomy of the rectum and pelvic colon, and the importance of directing the sigmoidoscope along this anatomic course is a requisite factor to the performance of these examinations.

Experts have long regarded blanching of the mucosa as a sign that too much pressure is being exerted and as a warning that the instrument should be withdrawn from this point and reintroduced. Ultra-cautious physicians refuse to administer a barium enema or any type of enema following a sigmoidoscopy because of the danger of a possible unrecognized perforation. The prognosis for life is always much graver if an enema has been given following perforation. However, in the routine of many offices and clinics it is customary to perform a barium enema following the sigmoidoscopy so that the patient need undergo but one preparation for both examinations. When the sigmoidoscopy has been performed by a competent individual, in the absence of untoward symptoms, it seems reasonably safe to follow with a diagnostic enema.

Frequently one encounters difficulty in passing the sigmoidoscope into the pelvic colon of highly neurotic and tense individuals. In these circumstances, the examination should be postponed or foregone unless regarded as absolutely essential; no forceful attempt to enter the sigmoid should be made. In instances of ulcerative colitis it is not always essential to enter the sigmoid; only in cases of suspected carcinoma must the examination be complete.

### DIAGNOSIS

It is of utmost importance to make the diagnosis of perforation of the colon promptly. This, however, not always is possible; in many instances the examiner does not know when he has perforated the bowel wall; he is only warned of the accident by the patient's reactions. In certain instances the diagnosis can be made on objective evidence. Lockhart-Mummery (8) quotes the case of a physician who, upon removing the obturator, and looking through the sigmoidoscope, found his eye focused on a viscus which upon closer scrutiny proved to be the gall bladder. This is an unusual experience, yet others have similarly seen appendices epiploicae, the glistening surface of the peritoneum, or have noted peristalsis of the small intestines through the sigmoidoscope. Occasionally the rent itself has been seen or the rush of air upon respiration has been heard, giving evidence of the presence of a perforation. Bleeding is usually not observed and cannot be depended upon as a significant sign. A very valuable diagnostic sign is afforded by a flat X-ray plate of the abdomen in suspected cases. Air will be seen under one or both domes of the diaphragm in practically every instance. This examination should not be omitted in a case suspected of perforation during sigmoidoscopy.

The diagnosis on the basis of subjective symptoms is variable, the symptoms being of two types. Most patients complain immediately of sudden agonizing abdominal pain of such severity as to require repeated doses of morphine. Pain in these cases is soon followed by symptoms of peripheral circulatory failure, pallor, cyanosis, rapid, thready pulse and other familiar

symptoms of shock. This striking and dramatic sequence fortunately occurs in most cases of perforation and leaves no doubt that peritoneal shock had occurred. A smaller group of patients will manifest no discomfort at the time of the examination and will often leave the physician's office entirely unaware of any unusual circumstance, only to be seized with severe abdominal pain 12 to 24 hours later. Upon examining the patient at this time the signs and symptoms of peritonitis will usually be well marked. Under expectant treatment it is extremely rare that any patient who has suffered a perforation of the colon will escape peritonitis either general or local, and eventually all give the classic symptoms of this complication.

### TREATMENT AND END-RESULTS

Upon the recognition that a perforation has occurred during a sigmoidoscopy or other intra-rectal manipulation, there should be no delay in transferring the patient to the operating room. The type of operation will depend upon the discretion of the surgeon at the table. In cases in which there has been no delay, simple closure of the perforation has been successful. The procedure in "delayed" cases complicated by an active peritonitis cannot be bound by generalization and each case must be treated according to its own indications.

Records were obtained of 58 cases of perforation of the large intestine in the course of sigmoidoscopy or other intra-rectal manipulations. Of this number, 30 were reported in sufficient detail to enable derivation of certain facts regarding prognosis. Of these 30 cases, 24 were operated upon, laparotomy with closure of the perforation being done in each case. The mortality for this group of operated cases was 50%. Against this the mortality of the six unoperated cases was 66.6%. In 18 of the 24 operated cases the time interval between the examination and the operation was reported. Of this number 13 were operated upon within 7 hours of the accident; 7 lived and 6 died, making a mortality of 47%. The 5 remaining cases were operated upon between 7 hours and 72 hours after the perforation; the mortality in this group was 100%.

### SUMMARY

1. Perforation of the sigmoid as a result of diagnostic and therapeutic manipulation is not infrequent. 25 reported perforations in the experience of 28 physicians reveals it not as a rare occurrence.
2. Immediate recognition of the accident is mandatory in order to save life.
3. At best, with immediate operation, only 50% can be saved.
4. The trauma is not necessarily dependent upon a pathological process in the colon.
5. The accident does not necessarily imply faulty instrumental technique.

### REFERENCES

1. Cooke, H.: Traumatic Rupture of the Intestine. *Ann. Surg.*, 45:321, Sept., 1932.
2. Numbaugh, M. C.: Traumatic Perforation of the Sigmoid. *Penn. Med. Jour.*, 35:712, July, 1932.
3. Madelon, O.: Impalement Wounds of the Rectum and Colon. *Arch. Clin. Chir.*, 137:1, 1925.
4. Andrews, C. W.: Quoted by Yeomans in "Proctology," Appleton, 1929.
5. Schmidt, Adolph: Perforation of the Rectum by Proctoscopy. *Muench. Med. Wochsch.*, 59:1154, May, 1912.
6. Dick, W.: Injuries Caused by the Passage of Sounds Into the Rectum. *Brit. z. Klin. Chir.*, 159:174, 1934.



7. Buie, L. A.: Proctoscopic Examination and the Treatment of Hemorrhoids and Anal Pruritis. Mayo Clinic Monograph, Saunders, 1931.
8. Lockhart-Mummery, P.: Diseases of the Rectum and Colon, 1923. Note. Following are references from which case reports were obtained: Yeoman, F. C.: "Proctology," Appleton, 1929.
- Behrend, M., and Herrman, C. S.: Traumatic Perforation of the Sigmoid Colon. *J. A. M. A.*, 101:1225, Oct., 1933.
- Goldman, C.: Rupture of the Rectum During Proctoscopic Examination. *J. A. M. A.*, 93:31, July, 1929.
- London Correspondent: Fatal Use of the Sigmoidoscope. *J. A. M. A.*, 78:829, 1922.
- Menegaux, G.: Serious Accidents with the Sigmoidoscope. *Presse Med.*, 41:1957, Dec., 1933.
- Retzlaff, O.: Perforation of the Rectum Due to Rectoscopy. *Muench. Med. Wchsch.*, 59:1669, July, 1912.
- Rayner, H.: Injury of the Rectum Caused by Faulty Administration of an Eaema. *Brit. Med. Jour.*, 1:419, 1932.
- Brumbaugh, C.: Rupture of the Rectum Resulting from Instrumentation. *Atlantic Med. Jour.*, 27:651, July, 1924.
- Strauss, H.: Procto-Sigmoidoscopy. Leipzig, 1910.
- Gaet, S. G.: Diarrheal, Inflammatory, Obstructive and Parasitic Disease of the Gastro-intestinal Tract. Saunders, 1915.

### DISCUSSION:

DR. CHARLES GORDON HEYD (New York City):

It is fortunate that from time to time we have an appraisal of certain commonplace diagnostic methods. I am always impressed in going to the scientific session to see complicated or simple instruments being sold to inadequately trained men, under high pressure salesmanship.

Many individuals will pass a sigmoidoscope who certainly wouldn't attempt to pass a bronchoscope or laryngoscope, and there is a tendency with our armamentarium of diagnostic procedures for men inadequately trained to attempt diagnostic manoeuvres that are inherently associated with some danger.

I think a distinction must be made in sigmoidoscopy in the normal or alleged normal colon and one that is the site of the disease. By analogy it is difficult to perforate a normal uterus, and it is easy, extremely easy, to perforate a pathological uterus, and again here is a great clinical demarcation that the perforation of the normal rectum or sigmoid will be associated with almost an immediate agonizing pain, whereas the perforation through a diseased sigmoid or upper rectum may not be associated with an immediate agonizing pain.

At four o'clock in the morning a patient at Post-Graduate Hospital had a sudden agonizing pain. The previous day he had been examined by some six or seven individuals. Here again a warning should be uttered against the diagnostic exploitation of individuals. There is always some trauma in introducing the finger, and certainly in introducing an instrument. The patient was given some morphine, and here you have one of the ironies of medical accident. After a primary misadventure, there is a sequential list of further accidents.

The house doctor, not appreciative of the possible danger, ordered a colonic irrigation, and three quarts of a solution was given and about a pint returned, and still that didn't occasion very much inquiry; but at two o'clock in the afternoon, upon doing a laparotomy, the remaining two and a half quarts were found free in the abdominal cavity.

After a perforation occurs, the circumstances are set in motion for a peritonitis, and while it may be somewhat irrelevant to take up some of the surgical phases, I should like to bring to your attention certain recent contributions on the physiological mechanism of perforations and peritonitis, and particularly to suggest that you read W. Sampson Handley's paper on "The Treatment of Diffuse Peritonitis." (*British Journal of Surgery*, 12:47, 1925).

When a bowel is perforated, either grossly by instrumentation or minutely by a pathological process, there is first a transudate which rapidly becomes an exudate. From these initiatory pathological changes there follow in rapid sequence: (a) an increase in the severity of the pathological reaction, (b) further attempts to arrest the spread of the infectious process by walling off, and (c) a breaking through of the barriers of the local peritonitis and the development of a progressive spreading, diffuse peritonitis.

Handley is of the opinion that intestinal obstruction is the outstanding feature in the death producing mechanism. In his paper he illustrates what he terms "ileus duplex," and demonstrates that intestinal obstruction occurs first as involving the terminal ileum and secondly as involving the sigmoid or intestinal colon. Dr. Handley advocates, therefore, as the treatment of this condition: (1) an anastomosis between the highest jejunal loop and the transverse colon as a means of overcoming the small bowel obstruction, and (2) a cecostomy to drain the large bowel. In our limited experience with this operation it has been most successful.

DR. JOHN L. KANTOR (New York City): It was stated that a knowledge of the anatomy was necessary to safeguard one against accidents in these cases. I don't think a knowledge of anatomy is of any great importance. If you think back to the days before we had electrically lighted instruments, you will recall being taught something like this: You introduce this proctoscope blindly, go two paces to the left, one to the right, three to the front, and so forth. As a matter of fact, you were actually guided by the patient's screams in your introduction, and not by anatomic knowledge.

What one really needs is one's eyes and a certain amount of judgment and experience. A proctoscope should be introduced under the guidance of the eye. As soon as the sphincter is passed, the need for the obturator is over. It is withdrawn and one uses the light and looks.

I think air inflation is used rather frequently and I wish to point out that air inflation is not desirable in the introduction of proctoscopes. What one needs is air, but that is provided for by the proper posture as was taught by Sims in pelvic examinations.

Next, to find the lumen ahead of the introducing instrument, it is wise to make use of long applicators, longer than the instrument, 12-inch applicators for 10-inch instruments. We provide these wooden applicators with cotton tips, and push ahead very gently to find the lumen.

Dr. Soper, of this Association, pointed out the relaxing value of magnesium sulphate. The applicator is soaked in a 25 per cent solution of magnesium sulphate and allowed to sink in and find its own way into the lumen.

Next comes the question of kinks. A kink is probably due to congenital bands or to adhesions. To my mind, it is very risky to try to go beyond a kink that cannot be readily passed. When such a kink is encountered, one had better call it a day and stop.

Now, the indications for proctoscopy are twofold. We look for either ulcerations or for cancer. If we are looking for ulcerations, we have usually seen enough when the first patch of diseased mucosa is reached. There is no advantage in going further.

In cancer suspects one would like to go the whole length, and heretofore it was important to do so. The old X-ray method left one in a fog, but now we have the oblique position of Stewart and the double contrast enema. These eliminate the need for taking undue risks with the proctoscope.

DR. BURRILL B. CROHN (closing the discussion): Scientific work requires an unbiased viewpoint and an impartial reporting of the findings and procedures in a given situation. Facts must be faced, not dodged. Frankness in difficult situations is always instructive and must eventually lead to the avoidance of the conditions which tend to lead to accidents.

Fifteen years ago, while performing a sigmoidoscopy upon a normal individual with a normal sigmoid and a cooperative patient, I was amazed to see the glistening peritoneal coat of the small intestine; I had been using no undue force, and was aided only by air inflation. The realization of what had happened prompted immediate operation, with fortunate complete recovery by the patient. For twelve years succeeding this mishap, several sigmoidoscopies a day were a regular routine.

Three years ago, in again a normal cooperative patient, some trauma must have resulted sufficient to give rise to a localized peritonitis. In this instance the patient left the clinic without complaining; only some weeks later did I hear of the result of an exploratory laparotomy.

Dr. Heyd mentions the subject of enemas following traumatic perforations. Any type of enema after perforation will materially increase the danger to the patient. There are however, instances where enemas have been given without fatal results, to-wit; I had the privilege of examining the following case:

Six or eight years ago a workman, while leaning over his bench, was approached by his associates in the shop and a pneumatic air hose was inserted into his rectum. He was examined by the company doctor at the time, who assured him nothing had happened to him and he was perfectly all right. He was given castor oil and was sent home and told to take an enema. Several enemas were given in twenty-four hours, and the man not improving,

he was taken to the Post-Graduate Hospital and was operated upon. He made an uneventful recovery.

In another case recently the fulguration of a polyp resulted in localized peritonitis under the diaphragm. The patient made an uneventful recovery.

The cases we have collected, twenty-five by questionnaire from the members of the American Gastro-Enterological Association advise us of the fact that perforations do occur and must be immediately dealt with. The seven-hour deadline seems to be very important. The 100% mortality after the seven hours seems very significant.

There is one more point I should like to make and that is that two of the largest clinics in the country reported they have no perforations. Whether perforation by a sigmoidoscopy is always avoidable I am not quite sure, but with extreme caution and care and being appraised of the dangers of the procedure, we may, in the future, possibly avoid all further perforations.

## Annual Abstracts of Protologic Literature

(May, 1934-May, 1935)\* By CLEMENT L. MARTIN, M.D., Chicago, Illinois

### ANATOMY

The investigations of various men doing post-graduate work in proctology at the University of Pennsylvania have given the following results: Confirmation of the presence of the "recto-sigmoid" one of the three arteries arising from the superior hemorrhoidal trunk, described by Pope in 1929; the demonstration by "duco" injections of lymphatic connections crossing the pectinate line; a posterior intersphincteric triangular space between the diverging fibers of the external sphincter (Brick's space) was demonstrated; the position of the branches from the inferior hemorrhoidal artery entering the posterior anal quadrant, described by Heller, was found to be approximately as defined by him. As to the sinuses reported by Hellwig, Tucker and Pope "they were partially demonstrated in a few specimens during routine examination in 1930, 1931, 1932, but credit should be given to these western workers since ours was incomplete and unpublished. At no time however were squamous cells of the stratified variety noted in our specimens, nor did we prophesy as to the importance of these ducts." In another study no longitudinal muscle fibers were found in the middle valve of Houston.

Through their examination of 161 patients, the recto-sigmoid junction, that vague and variable landmark, is located more definitely; they conclude, that although not exactly fixed it may be taken as being 6.6 inches from the anal margin, 5.4 inches from the ano-rectal line, 3.4 inches from the inferior valve, 2.2 inches from the middle and 1.4 from the inferior valve.

Milligan and Morgan describe the external sphincter ani as a trilaminar muscle consisting of a subcutaneous, superficial and deep portion. They describe the internal sphincter ani as a tubular muscle encircling almost the whole length of the anal canal. The inner surface of this ring is covered with mucous membrane, they state.

### AGRANULOCYTOSIS

This disease remains a matter of discussion. As to whether it is a definite disease entity, Jackson and Parker

state that discarding the extreme leukopenia secondary to sepsis, aleukemic leukemia, aplastic anemia, pancytopenia and leukopenias of certain metastatic bone tumors, arsenic, gold, and benzol poisoning, there remains what for lack of a better term may be called agranulocytosis, agranulocytic angina or idiopathic malignant neutropenia. . . . It is probably a disease entity.

Extreme leukopenia and neutropenia alone do not constitute valid criteria for the establishment of a single disease. Acute leukemia in the aleukemic phase may easily be mistaken for agranulocytosis, and agranulocytosis may shade into pancytopenia.

Cause: Amidopyrine is chiefly indicted. Madison and Squier, who first reported the drug as a cause, emphasize its important place in the disease, on the basis of further evidence. Although Kraeke and Parker state "acetanilid can be ruled out as an etiological drug since there is no report of any case of granulopenia following the use of that drug alone," such cases were subsequently reported by the preceding authors. Dinitrophenol is reported by Dameshek and Gargill as another causative drug, and the barbiturates by Hertz. Fitz-Hugh lists 31 preparations containing amidopyrine, among them Allonal, Amytal Compound, Cibalgine, Neonol Compound, Neurodyne, Peralga and Pyramidon. The exact chemical structure of the responsible agent remains undetermined, suspected are the benzene ring, both the (NH) and (NH<sub>2</sub>) radicals and (NO<sub>2</sub>).

Jackson and Parker believe that overwhelming infections are the result rather than the cause of the disease. That allergy is of major importance has yet to be shown. Endocrine disturbances are questionable. Madison and Squier believe that those "who have developed allergic or anaphylactic hypersensitivity to amidopyrine" have the disease.

Amidopyrine and related drugs are of etiological importance in some cases but in other instances there is no such explanation.

Fisher presents two cases of agranulocytic angina in his article, one of which had barbiturates and amidopyrine, the other did not. He considers the latter "therefore belongs to that group of cases in which no etiologic factor can be determined."

Lotze studied cases of acute and chronic arthritis treated with amidopyrine to determine unfavorable secondary effects. In 5 cases the drug caused decreased diuresis.

*Editor's Note*—\*The annual compilations of important advances in Proctology arranged for the members of the American Proctological Society and published by that society for the convenience of its readers. To the Executive group of the society, as well as to the society's official Supervisor of Abstracts, Dr. Clement L. Martin, the Journal and its readers are indebted for the courtesy of here printing the abstracts. This annual survey of this special field of diagnosis and surgery appears elsewhere only in the Official Transactions of the American Proctological Society.

This change was reversible. One fatal case had marked amidopyrine intoxication and central nervous system manifestations. Predisposing factors he thinks were largely responsible for the effect in this case. His experience inclines him to continue the use of the drug in arthritis.

*Treatment:* As the exact etiology and pathology are still *sub judice*, diagnosis and therapy remain no more certain. As usual in such conditions general nursing care and hygienic measures are important. To stimulate bone marrow to produce granulocytes (to prevent maturation arrest of white blood cells at the stem stage), *Kracker* used 5-10 drops of turpentine as intramuscular injections,

*Henry Jackson* favors injections of pentonucleotide intravenously and intramuscularly. *Wm. P. Murphy* uses liver extract with good effect, *Dameshek* and *Gargill*, adenine sulphate.

Although the general condition of the patient, the oral lesion and blood picture are the striking aspects of this disease, as well as the almost invariably fatal termination, the subject has been again reported in a review of proctologic literature because of the anal or rectal ulceration which occurs in the occasional case. Blood studies in the unusual anal ulcer are advisable as well as caution in the use of certain post-operative analgesics.

## SECTION VIII—Editorial

*NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastroenterological Association is in no way responsible for editorial expressions.*

### THE GREAT VALUE OF SOME PHYSIOLOGICAL OBSERVATIONS ON MAN

THERE are many occasions when a surgeon operating under local or regional anesthesia can make observations of tremendous value to clinicians, and particularly to gastro-enterologists. Any internist with a large material is seeing every month patients with abdominal pain that has not been relieved by one or more operations on appendix, gall bladder, pelvic organs, or stomach. Sometimes, then, the question arises, can anything be accomplished by interrupting the pathways of pain? Can they be cut or would it be possible in the case of mixed nerves to apply alcohol which can block sensory impulses without causing too much injury to efferent fibers?

One great difficulty in the way of attempting this sort of thing has been that, after all these centuries of anatomic research, neither the anatomist nor the physiologist nor the neurosurgeon always knows exactly where to cut. Doubtless much knowledge will come, but it may be that always there will be some doubt and difficulty because the pathways in man are somewhat different from those in nearly related animals, and worse yet, the pathways in one man are likely to be somewhat different from those in another. Even more perplexing is the fact that when the normally used pathway is interrupted in a highly sensitive person, new paths sometimes will form in order that the patient can go on with his torture.

With these thoughts in mind, it is particularly stimulating to find notes like those published recently by *Adson* (Proceedings of the Staff Meetings of the Mayo Clinic, 10:623-624, 1935) who, while operating on an intelligent man under spinal anesthesia, laid bare the splanchnic nerves and the celiac ganglion. It is well known that in dogs, the splanchnic nerves are exceedingly sensitive to injury, and it is thought that most sensations of pain coming from the upper abdomen reach the brain along these two big pathways. In the patient operated on by *Adson*, the mere sponging of the splanchnic nerves with a small cotton tampon produced excruciating, lancinating pains in the posterior axillary line, radiating from a point below the angle of the scapula upward to a point corresponding with the upper level of this bone. Stimulation of the lesser and minor splanchnics caused pain in the lower

part of this area, while stimulation of the major splanchnic nerves caused pain more in the upper part. Compression of the celiac ganglion produced pain radiating to the region of the right shoulder, while compression of nerve fibers peripheral to the ganglion caused aching pain in the right lower part of the abdomen. All these pains were blocked by injections of the splanchnic nerves with procaine.

It may well be that, in some cases of intractable duodenal ulcer, more relief will eventually be given by splanchnicotomy than by gastro-enterostomy or pyloroplasty. Fortunately for gastro-enterology, a number of neurosurgeons are now following the lead of *George Brown* and *Adson* and in many cases are cutting splanchnic nerves in order to relieve hypertension. It may be that, in this group of patients, can already be found one or more who, in addition to the hypertension, had pain in the upper abdomen. In that case, what we who are interested in painful intestines want to know is: was there relief from the pain?

It would be very helpful if readers who have made observations like those of *Adson* would send in short notes for publication in this Journal.

Walter C. Alvarez.

### THE ETIOLOGY OF PEPTIC ULCER; A REVIEW OF ONE THEORY

WE have just read with some interest an article by *Samuel C. Robinson, M.D.*, in the August, 1935, number of this Journal, bearing the title: "On the etiology of peptic ulcer—An analysis of 70 cases."

We are frank at the outset in stating that we are disappointed in the Author's conclusions, which, being made to rest upon the so-called "neurogenic" theory do not satisfy the demands of an enquiring mind.

We are heartily in agreement with his view, however, that many so-called factors of etiology that have heretofore been brought forward have nothing whatever to do with the origin of peptic ulcer.

Let us review this article in some detail, as the subject well warrants an impartial discussion of the observations that have been made—whether they be enlightening or confusing.

The Author is quite sound in his reasoning that peptic ulcer does not occur in the lower animals and

shows keen judgment in quoting Mann's opinion that "Chronic peptic ulcers have never been consistently produced experimentally in the gastric mucosa by any method." This premise, we believe, is of genuine importance and one upon which we can stand firmly and safely.

We believe that the lower animals do not develop peptic ulcer because their habits of living are natural, and just in so far as these habits are maintained, do they remain free from many a disease to which man is heir by reason of his being "civilized," as we say.

Peptic ulcer occurs very rarely in the Negro and in the lesser pigmented races, claims the Author. This is equally true of pernicious anemia, leukemia, coronary disease and diabetes mellitus—just to mention a few other diseases.\* So why should we think of this rarity of incidence as showing "a unique selectivity in the annals of disease"—to quote from the Author? If he must theorize as to the Negro in his apparent exemption from many diseases prevalent among the white race, let him recall how little is known regarding immunity to disease, natural and acquired, not only as to races, but also among families and related individuals.

For the white race, "a highly competitive and more complex civilization has made existence more precarious, and those who are on the firing line of this life-struggle, such as salesmen, specialists in all fields, particularly medicine, executives, etc., are more prone to this disease." So states the Author in laying the foundation for the neurogenic theory, but why doesn't he let his 70 cases bear him out in this contention, and why hasn't he a high percentage of his ulcer-patients arising among say those who drive the mighty steeds of the 20th century between Chicago and New York?\*\*\*

We believe that if Dr. Robinson had had any really significant figures to produce in his argument, he would have published them.

As to the question of "the ulcer build" we do not feel at all impressed by the finding that the victim of peptic ulcer belongs to the "long and lanky type." Isn't it just as logical and true to state that he is long and lanky because he has an ulcer? There probably comes to him an ability to handle his foods in such a way that he does not store body-fat and as a consequence he remains "linear" rather than becomes "lateral." There are probably many abnormal conditions within the body which may lead to the long and lanky type of individual, but ulcer is only one of many such pathological states. And to bring the personality of our ulcer victim into the picture does not elucidate the problem at all, but we believe merely shows the reaction of his temperament to the presence of his ulcer, just as any other disease of chronicity stamps itself upon the mentality of its subject in its own peculiar way. It is in this manner that all chronic disease leaves its impress upon the plastic tissues of the "mind."

\*Not quite so true as was suspected formerly, now that Negroes are being carefully studied by competent clinicians in modern hospitals. Ed.

\*\*\*Robinson includes no patients of the last named, but records of various institutions indicate that railroad, engine drivers are by no means free from peptic ulcer; how much bearing their occupation has upon the production of their ulcers, one can but conjecture. Ed.

We next proceed to consider the so-called ulcer-bearing area of stomach and duodenum as the *locus minoris resistentiae*. That the Author brings forth any evidence or proof why the peptic ulcer should develop within this limited area we cannot convince ourselves.

Dr. Robinson states that "the lesser curvature of the stomach which is the site of over 98% of all gastric ulcers receives most of the innervation to this viscus, etc." "This is the portion of the stomach that will receive the blunt of psychic trauma with the resultant hypermotility, hypersecretion, hyperchlorhydria, hypertonicity and vascular spasm." Except for the threat of an impending disaster as voiced in these high-sounding words we fail to discover a pathological basis for the development of ulcer in an area so richly supplied with nerves and blood-vessels. So long as ignorance continues to hide under terms as obscure as "psychic trauma," progress in medical investigation will continue to languish.

The Author's assumption of thrombosis for the true etiological basis of the incipient and chronic ulcer we accept as being well founded, but to attribute this thrombosis only to vascular spasm is not altogether satisfying in view of what we find by way of changes within the walls of these blood-vessels. As far back as 1883 Hauser, by his careful work upon the blood-vessels in and near peptic ulcers concluded that: "The hemorrhagic infarct is followed by a chronic ulcer, only when the disturbance in circulation follows local disease of the blood-vessels. The degree of vascular disease, therefore, determines the more or less chronic character of the ulcer."

Whence these vascular changes?

Shall we continue to accept as a Heavenly pronouncement the thread-bare theme of "over-work, stress, strain and worry"?

Shall we be influenced too far towards a "neurogenic" theory in our conception of peptic ulcer by the finding of a perforated ulcer in association with brain-tumor? Have we not seen perforating ulcers associated with chronic cholecystitis or other diseases of long standing? Why not blame the one on the other? Or, why not say in equal fairness of mind that what caused the ulcer likewise was responsible for the origin of the brain-tumor, etc.?

Are we venturing too far afield to look for a solution of the problem in the study of the relation of foods and poisons to certain degenerative changes in the vascular system?

The 16th Hektoen Lecture of the Frank Billings Foundation, by Timothy Leary, M.D., recently has been read with absorbing interest and the subject-matter contained therein doubtless will bear much fruit in our future conception and study of disease in the broadest sense.

It may lead us back to some fundamental considerations which apparently have slipped our minds. For instance: that a man is as well and as sane and as young as his arteries are free from disease, and that the degree of arterial disease is just, and justly, the expression of the distance he gets from the proper choice and use of that which entereth into the man.

Maurice B. Bonta, Los Angeles, Calif.

## SECTION IX—Book Reviews

(This section is open to contributions from any medical reader, whether or not a member of the Editorial Council).

*The Management of Colitis.* Dr. J. Arnold Bargen. National Medical Book Company, New York, 1935. 233 pages, price \$3.00.

THIS volume gives a comprehensive view of the whole problem of colon disease both organic and functional. Starting from a basis of anatomic and physiological principles, the normal function is first considered, then the etiology, pathology, diagnosis, complications, and treatment of the following conditions: Chronic ulcerative colitis, amoebic colitis, tuberculous colitis, mucous colitis or irritable colon, and finally a group of conditions to be distinguished from colitis.

The most extensive discussion is of ulcerative colitis in which field the Author has contributed so much. An enormous experience covering some 1500 cases at the Mayo Clinic permits him to speak with authority. Details of the bacteriological findings and the cultural methods in isolating the diplococcus, which Bargen regards as more or less specific in the etiology of the disease, are given in detail. He does not accept the idea that bacillary dysentery plays any primary or important part in the etiology of chronic ulcerative colitis. Whether or not one accepts the specificity of the "Bargen diplococcus" as the cause of the disease, one must have a great deal of respect for the results the Author has been able to obtain at the Mayo Clinic in a large series of cases.

Complications of ulcerative colitis are fully discussed with their relative frequency on a statistical basis given in detail. Considering the large amount of ulcerating surface, complications are relatively infrequent. Only about 15% of all patients have any complications although those who are so afflicted often show numerous complications. Perirectal abscess is one of the earliest and most frequent lesions to accompany the disease. Stricture of the rectum or colon was originally second in frequency but has been much reduced by modern treatment. Other septic complications such as endocarditis, (1%), arthritis, (4%), erythema nodosum, and uveitis occasionally occur. Abscess of the liver is extraordinarily rare as is also pyelitis despite the fact that we often attribute pyelitis to infection from even the normal colon. Carcinoma occurs in approximately 2½% of the cases most commonly associated with polyposis which is found in at least 9% of cases. Skin sloughs and lesions of the type of *pyoderma gangrenosa* are associated with ulcerative colitis more than with any other one condition.

Treatment has been well standardized by the Author and includes general measures in regard to diet, vitamins, rest, drugs, blood transfusions as well as specific therapy. The specific serum is obtained by immunizing horses against many strains of the diplo-strep-

tococcus. In the more severe cases this serum is given intravenously; routinely it is given by deep intramuscular injection after desensitization by intracutaneous injections. The vaccine is used in the more chronic cases. Irrigations are in general condemned although on special occasions very bland or mild antiseptics are used. Removal of foci of infection is stressed.

In the occasional case in which all medical measures have failed or in the presence of an acute emergency, such as uncontrollable hemorrhage (1% of cases), surgical treatment is considered. Ileostomy is the treatment of choice and may be a life saving measure under certain circumstances. It may however have to be a permanent fistula and this should be considered by the patient before operation. Subsequent anastomosis is difficult and may be impractical after a period of months on account of stricture formation or persistent ulceration. Even in the most favorable cases the disease may relapse after an apparent cure. The practical management of the ileostomy is considered in detail and the Huffer bag is regarded as the most suitable device for the purpose.

Excellent illustrations supplement the descriptive matter. In this connection, also case histories and personal experience of patients with permanent ileostomies are of special interest. The psychological adjustment of the patient to the artificial anus is discussed. Occasionally colectomy may be advisable and should be done about six to eight weeks after ileostomy.

Some experimental work is described including kymographic records obtained by balloons in the isolated colon in animals and in patients with ileostomy or colostomy. The cecum is the most motile portion of the colon, having three distinct types of movement. The distal colon, normally quiescent, is most easily activated by the stimulus of food in the stomach, the so-called gastro-colic reflex.

Amoebic and tuberculous colitis are also considered quite fully including the differential features clinically and radiologically. The final diagnosis rests upon bacteriological and microscopic findings. Practical methods for finding and identifying the amoebic cysts are given.

Finally, the Author has a lengthy discussion of so-called "mucous colitis," listing its many synonyms and also the various forms and conditions of irritable colon. Among the prominent causes of this colonic dysfunction he lists overwork, overeating, insufficient rest, nervous fatigue, nervous tension, exposure, local irritation caused by laxative, and colonic irrigations, foods and the bacteria that are normally present. In treatment, the principle of blandness in food and medication is approved in general and as in ulcerative colitis, colon irrigations are mainly mentioned for con-



demnation. Neurogenic and psychic factors are stressed at length. In the diagnosis of these disorders, food allergy and the colon complications of such systemic diseases as sprue, pellagra, anemia, exophthalmic goiter, uremia, etc., are discussed.

Altogether the book presents a very useful compila-

tion of the present day knowledge of the vexed problem of colon disease from the standpoint of differential diagnosis and the practical management of patients especially with the intractable forms of ulcerative colitis.

V. C. Rowland, Cleveland.

## SECTION X—After “Hours”

### Some Social and Medical Impressions of Moscow

By

CHAS. GORDON HEYD, B.A., M.D., F.A.C.S.  
NEW YORK, NEW YORK

SOVIET Russia represents a country of approximately 160,000,000 people. It occupies nearly one-seventh of the surface of the globe, and its nationals comprise various strains of some two hundred races, expressing themselves in something over sixty different languages. Any evaluation of the social and medical status of Soviet Russia must be made upon a knowledge of its pre-revolutionary status. Russia was a country pre-eminently agricultural, definitely deficient in industrial development, burdened by an autocracy of complete domination, with a spiritual background of superstition and mystery, and made up to a large extent of a dull, illiterate, slave-driven proletariat. Such was the background of Russia before the Revolution.

Any preconceived ideas that a first visitor may have had of Russia were rapidly changed upon arriving in Moscow. There was no evidence of starvation, and rarely a beggar. (Fig. 1). The people one met and passed upon the street apparently were happy, and although laughter and smiles were not common, one had no reason to believe that an urban population that on one day (Sunday) attended a football game to the extent of 70,000, had an attendance of 30,000 at the Jockey Club, and 100,000 at the “Park of Culture and Recreation,” representing in all some 200,000 people, was lacking in wholesome recreation and pleasure.

The personal impression of police surveillance, however, remained true, and the casual use of a kodak was only possible by express permission and with very evident restrictions. One did not see shelterless children nor homeless waifs, although everywhere at all hours of the day and night immense crowds of people seemed to be moving to and fro, apparently aimlessly. The entire population of the city of Moscow seemed to be dressed always the same, and almost always in the same way. There was practically no differentia-

tion between one woman and another, nor between one man and another. The use of rouge, lip stick, and hair adornments was restricted, according to my observation to the female employees in the three hotels set apart for the foreign tourist (August, 1935).

Perhaps the most constantly recurring impression that one received was that the Soviets were working like fury to develop a classless society and that all of their present activities were predicated upon some not too distant Utopian state of the future. Time and time again the traveler is lectured by his guides and informed, somewhat in the manner of the recitation of a ritual, of what the Soviets have accomplished, what they propose to accomplish, and how politically backward is the remainder of the world.

In the development of this so-called completely socialized state there occurred towards the end of the late World War a fateful juncture of four great forces. According to Chamberlain, these four great forces which made for the success of the Russian Revolution were: (1) the complete disintegration of the Russian Army, (2) the seizure of the land by the peasants, (3) the revolt of the workers in the industrial centers of Leningrad and later of Moscow, and (4) a separatist movement aroused by the enthusiasm for individualistic nationalism. The culmination of these forces provided the background for the surrender of Russia to the Germans, and gave Lenin the opportunity of applying his genius for revolutionary technic to the theories of Karl Marx, and of operating them by force for the alleged benefit of the 160,000,000 people living in Russia. Lenin and his co-workers proposed to liquidate all social and economic ills. In their opinion, accomplishment of this project necessitated (1) complete destruction of Czarism and its attendant evils, (2) destruction of capitalism and private ownership of property, and (3) destruction of the prevailing religion. The immediate effect of these three destructive influences was an almost complete annihilation of the intelligentsia—members of the professions,

\*Abstract of a Lecture before the Medical Society of the County of New York, January, 1934.  
Submitted October 24, 1935.



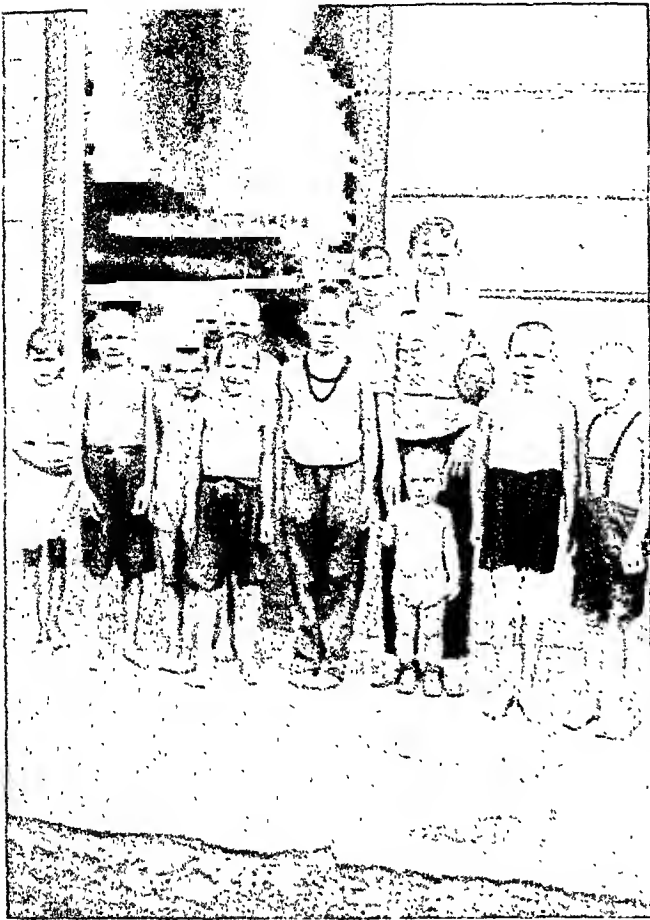


Fig. 1. Typical group of children as observed in the streets of Moscow.

lawyers, merchants, engineers and other technically trained citizens of the Czarist regime.

Since the historic Revolution, which began in March, 1917, and culminated definitely in the fall of that year, the postrevolutionary history of Russia embraces five distinct periods—The Revolutionary Period; 1917 to 1921: The War of Communism; 1921 to 1928: The New Economic Policy; 1928 to 1933: The First Five Year Plan; 1933 to date: The Second Five Year Plan.

All information obtained in Moscow by an American who does not speak or understand Russian fluently is entirely by the aid of and through interpreters. Apparently all the interpreters have memorized the particular speeches for each occasion, and fairly breathe revolutionary propaganda. They have the stock set of stories that all returning travellers tell, and particularly the one attributed to Stalin that there may be any number of political parties in Russia provided one is in power and all the others in jail. There is a common denominator for all the interpreters. Every feature that is objectionable in a capitalistic country is declared to be a social evil—illiteracy, poverty, prostitution, venereal disease, political enemies, churches, starvation—these are all social ills and can be "liquidated by the dictatorship of a proletariat." Time without number the word "liquidate" is used: to liquidate illiteracy, to liquidate the political enemies. In like manner "research" is used with the most extensive applications. Again, "scientific" is applied regardless of its original sense, so that in every interpretation the words "liquidate," "research," and "scientific" would appear repeatedly.

The spiritual level of character of any civilization can be determined by a consideration of two social factors: the rate of infant mortality, and the place occupied by women in the social scheme. Lenin wished to destroy every Czarist law which placed women in subordinate or humiliating positions, but that there ever was a nationalization of women or children is utter nonsense. Under Soviet legislation marriage is permitted solely upon the free will of the parties concerned, and marriages are either registered or non-registered. About seventy per cent of the marriages are registered, and divorce may be obtained at the desire of either party without previous notice, and without both parties being present. Yet the divorce rate in Moscow is, in 1933, less than in Chicago, and the divorce rate for the whole of Russia is one divorce to four marriages, while it is stated to be one to five in the United States.

Under the Soviet law there is no such thing as an illegitimate child, and in no country to my knowledge is the legal responsibility for children so onerous or so obligatory as in Russia. Either one or both parents are responsible for the financial maintenance of the children until they are sixteen years of age. Seventy-two per cent of the women between the ages of eighteen and fifty are workers, and have all the rights of men, there being no distinction in so far as working is concerned between the sexes.

The Soviet ideology is based upon the principle that women shall not be penalized because biologically they must be mothers, and every pregnant woman must cease working eight weeks before the birth of her

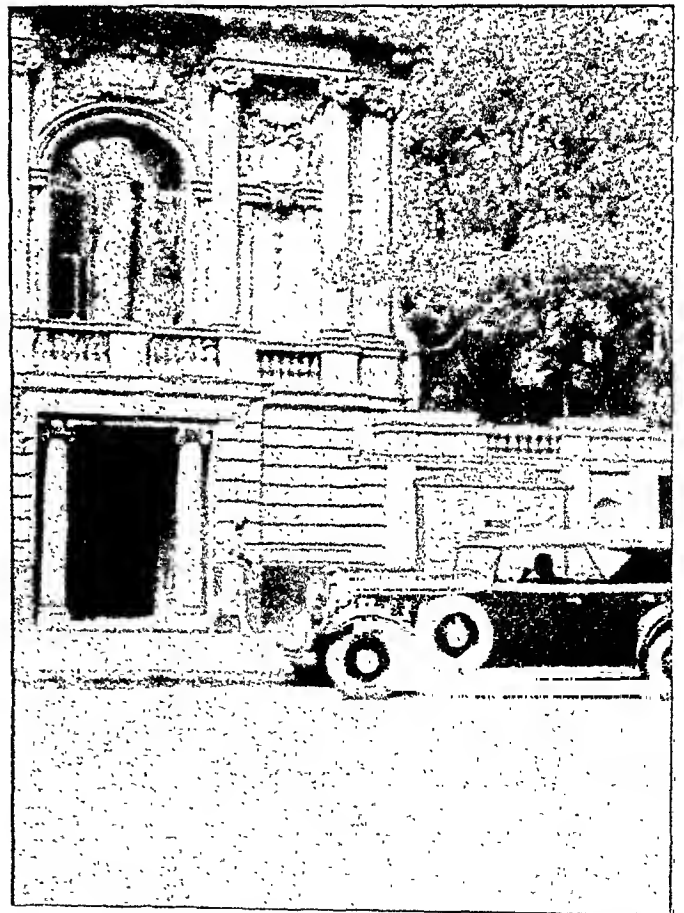


Fig. 2. Institute for Women and Children, Moscow: former home of Isadora Duncan, Dancer.

child and remain away from work for eight weeks after birth, representing in all sixteen weeks during which she receives her full pay as a laborer from the State Insurance Fund and from the factory. When she returns to work, she can only be employed on the first shift, from eight a. m. to three p. m., and doing light work. Practically one hundred per cent of the births in Moscow take place in medical institutions or hospitals. For the first three years of the child's life, the mother, if a worker, may avail herself of the so-called creches, or nurseries. The babies are graded by months into four age groups, aged respectively two to nine, nine to fourteen, fourteen to twenty-four, and twenty-four to thirty-six months. The Soviet authorities believe that the nurseries give the women the opportunity of taking part in the building up of the social structure. Special nurseries are for the casual traveler, the "show places" of Moscow (Fig. 2). However, like so many things one sees in Moscow, there is a tremendous discrepancy between the resources of the nurseries and their availability. Less than ten per cent of the children born in Moscow are able to receive the benefits of State-run nurseries.

Soviet philosophy believes that the fight against prostitution should not be against the prostitute, and the individual is neither penalized nor persecuted. The problem has been taken entirely out of the hands of the police and placed in charge of the social agents of the State on the assumption that prostitution is basically, economically, and socially an abnormality, the same as poverty, alcoholism, illiteracy, and crime, and that a new attitude of mind is more essential than laws.

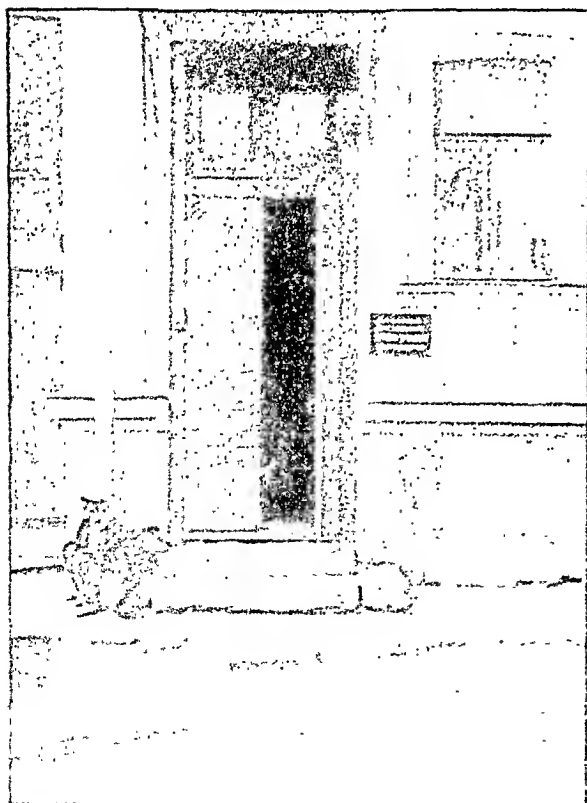


Fig. 3. One of the three Prophylactoria.



Fig. 4. The Abortion Clinic.

In the days before the Revolution there existed in Russia a so-called "yellow ticket." A woman engaging in prostitution voluntarily or otherwise registered with the police. She was given a yellow ticket, really a yellow folder containing her photograph and other personality and identity data. From that time forth she was forever a registered prostitute. It was told to me that there were thirty thousand registered prostitutes in Moscow before the Revolution. At the time of my visit the social agencies could only definitely allocate between four and five hundred women in the ranks of the professionals. If these facts are to be taken as literally true, the success that has attended this social war against prostitution might well invite the serious consideration of all capitalistic countries.

Shortly after the Bolsheviki came into power, they established what are known as prophylactoria (Fig. 3), where by request and probably command, these unfortunate individuals became "guests" of the government. About eighty per cent had one or both major venereal diseases, and practically all were in varying degrees of ill health. These women were given a complete health examination and their specific diseases treated. Necessary dental work was done. They lived from one to three years in a prophylactorium and after their health was somewhat restored to normal, they were placed to work on knitting machines, or given similar labor in a division of the prophylactorium. They made neckties, scarfs, handkerchiefs, shawls, and the like, and received the prevailing rate of wage as obtained in similar occupations, one-third of their remuneration being collected by the government to defray the cost of maintenance, one-third being taken up by contribu-

tions to trade unions and by State taxes, and the remaining third becoming the property outright of the worker. It was represented to me that there was very little if any restraint upon these women, that the occasional few who escaped or ran away always returned. When they were cured and discharged the women were already in possession of sufficient technical skill to earn a living. Most of them married and became good citizens, with few relapses.

It was stated to me on many occasions that the laxity of the marriage laws and the standard of the State administered abortion clinics were large factors in the suggested improvement in prostitution. For the medical man the abortion clinic, or abortorium, (Fig. 4), is the most striking of the presentations in Moscow. There is in every one of the main political subdivisions of Moscow an official abortion clinic, and any woman who is registered or non-registered in marriage, or any woman without the marriage status, can have an abortion performed at her own request up to the ten week gestation period, after which time she must carry through with her pregnancy. In August, 1933, there were 1,155 beds for abortion in the fifteen geographical subdivisions of Moscow. Twenty-one per cent of the women applying for abortion did not have registered marriages. The abortion service is the only medical service that in some measure is paid for out of the individual earnings of the patient. This fact is not without a relative economic importance. I was informed (with no way of verifying the facts) that in one district approximately 400,000 rubles were collected for the abortion service during the year 1932,

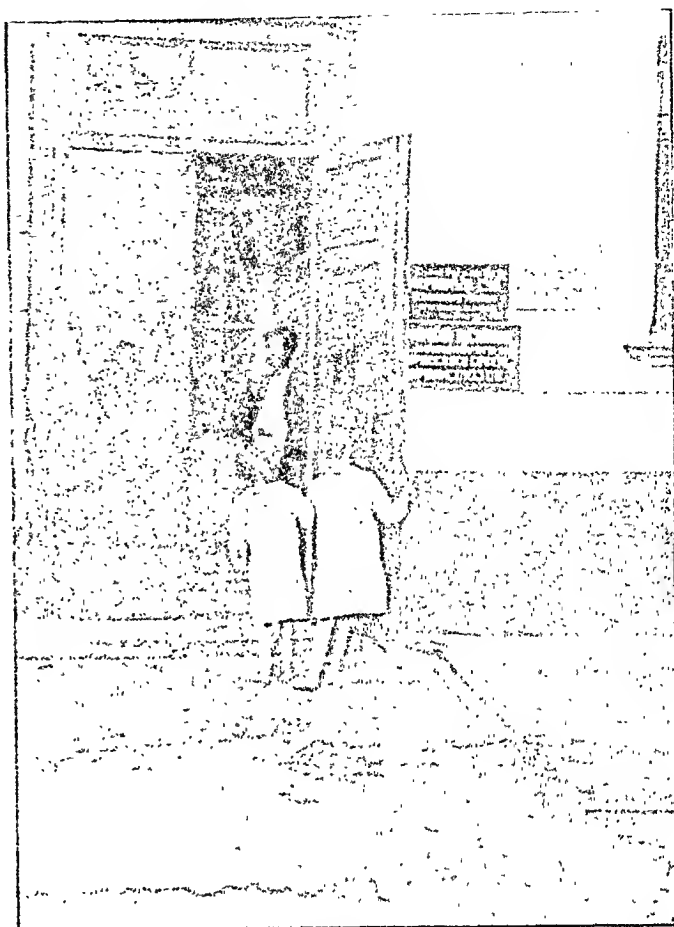


Fig. 6. The District Court.

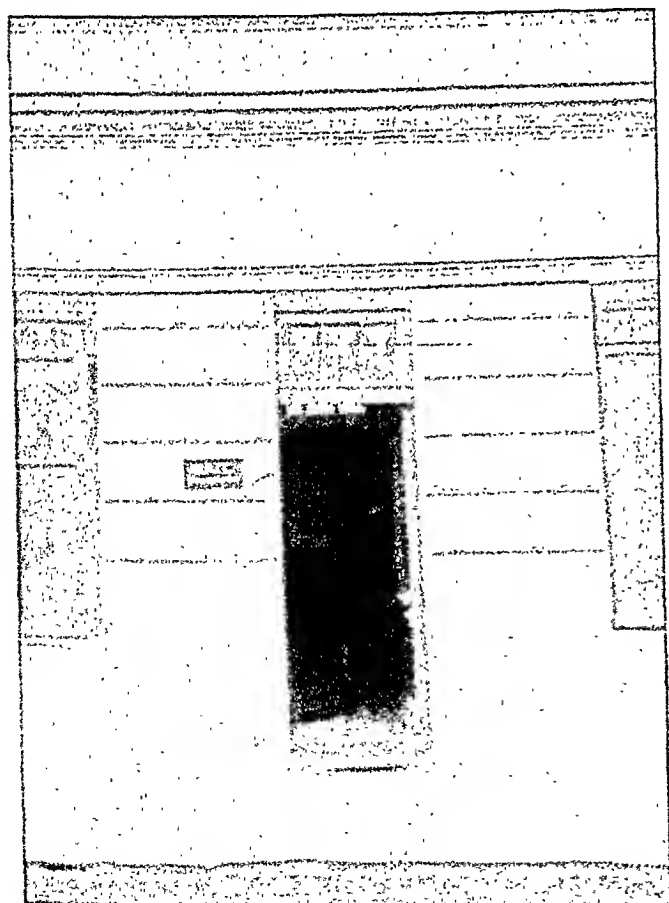


Fig. 5. "Zags," the Marriage Bureau.

that the disbursements by the government for salaries and overhead were 185,000 rubles, making an operative income of 215,000 rubles. Since the establishment of the abortion clinics the proportion of abortions has increased enormously, and in Moscow they were sixty-one per cent in excess of the normal births.

The Soviet ideology has as a background the principle of equal responsibility to its citizens, irrespective as to sex. The sexual relations in Moscow are more largely physiological than psychological. In all of the major districts there are contraceptive clinics. Sex information is frankly spread by every known device of propaganda—pamphlets, letters, books, exhibits, charts, lectures, etc. So far as one can observe there is no censorship on sexual information. There are texts and charts for the illiterate. Along the walls of the marriage Bureau, or Zags, Fig. 5, there hung any number of signs, two of which translated read as follows: "Don't forget before registering your marriage to consult a woman doctor on sex hygiene, contraception, and the future child"; "Any woman who wants to prevent conception should not depend on the man."

In regard to civil crime as opposed to political crime, one observes that the word "punishment" is everywhere replaced by the term "measures of social defense," and the maximum sentence for non-political crimes is ten years, the majority running for two to three years, and sentences of less than one year being usually remitted. There are no punitive measures for the correction of criminality in children under the age of fourteen, these children being placed under the pro-



Fig. 7. One of the few clinics; the so-called Railroad Clinic.

tection of the Institute for the Protection of Mothers and Children.

The courts (Fig. 6) are usually held in zones or districts presided over by three judges, the senior being appointed by the administration, and the other two by the labor union of the district. It is written into the criminal code that sentences must not cause the criminal needless suffering. There is a complete absence of lawyers. The system is one of class justice, and a worker, or a revolutionnaire, or the children of workers, receive special consideration as opposed to any of the former bourgeois class.

The Soviet philosophy in regard to disease and illness is very simple. It is held that illness is not primarily a personal responsibility, but as every citizen is an economic unit it becomes the duty of the State to restore the sick to well being, and to prevent illness. Medical practice, both curative and preventive, is one hundred per cent State medicine. In 1913, there were thirteen thousand physicians in the whole of Russia, and it was estimated in 1933 that there would be eighty-two thousand. Seventy-five per cent of the students in the medical school are women, and the social origin of the medical students is as follows: workers, 24.7%; peasants, 33.7%; hired farm laborers, 1.3%; employees, 40.3%. The percentage of workers and peasants in the medical schools is increasing each year. Eighty-five per cent of the students in the medical schools are members of a trade union. It is unquestionable that preference for admission to the universities and professional schools is undoubtedly given to the culturally lower strata of the population, and the univer-

sities are filled with students who are primarily ill fitted for higher education. The absolute State medicine imposed upon the entire country accepts the principle that one doctor is as good as another, a proposition that is manifestly false. In each zone is a point of medical consultation, and to this point comes the request for the visiting doctor. The physician makes the visit or sees the patient, and if a specialist is desired, the required specialist is called in. The patient may be treated at home, but is usually sent to a hospital or clinic (Fig. 7). The entire medical service is free, with the exception of the abortion service, and there is no such thing as personal choice of physician. Medical education is entirely under the control of the Commissaire of Health, and entrance to the medical school may be obtained in any one of the following ways: (1) the non-worker must have had from three to eight years of kindergarten and inferior school, and from eight to seventeen years of elementary and high school; (2) the worker in a factory may enter the medical school by attending a special workers' high school or Rabfac from three to five years, the last year of which he does not work at his trade, but receives a stipend from the government; (3) an individual may enter the medical school who has had a previous training as a nurse, a doctor's assistant, or as a graduate medical technician with three years of work in a medical institution. The result is a tremendous levelling process in education, with an almost ninety per cent preference for workers or children of workers. The universities are subject to an upsurging of students who are greatly handicapped by the absence of inherited or environmental educational advantages.

In the medical schools four types of medical instruction are given, and the medical student elects to enter one of the following: (1) The Faculty for Curing and Prevention of Disease—a five-year course with training for an internist, therapist, or surgeon; (2) The Faculty for Gynecology, Obstetrics, and Pediatrics—a five-year course; (3) The Faculty for Sanitation, Food Industry, Factory, and Sanitaria Practice—a course of four and a half years; and (4) The Faculty for Physiotherapy, and Mechano-Therapy—a five-year course.

The result of this medical educational system is to turn out an incompletely educated doctor, and to commit the medical student to the necessity of becoming a specialist, even while he is in attendance at the medical school. The system produces an extreme division in specialism. There is no uniform, all 'round medical curriculum. It recruits its members for class education. Basically there is a huge upswelling from below of incompletely educated students, and a tremendous accentuation of women in medicine. The system tends to reduce medicine to a trade in which medical practice is carried on as if it were a commodity, and it levels the economic status of the physician to a bare sustenance standard of living.

Yet at the same time the practice of medicine does offer in Soviet Russia one free day by law for every six days of work, and allows the individual to become a research worker or a hospital worker. For the first three years after leaving the medical school, however, the physician's time is entirely at the disposition of the Commissaire of Health. At the expiration of this three year period the doctor may take three years of study in one of a number of courses that will lead to

personal preferment and advancement along the road to a professorship. The success of an individual arriving at a professorship in medicine is largely dependent upon his energy and ability, his publications and research activities, together with the demonstration of his political regularity.

It is utterly impossible to apply the conditions of medical practice in Soviet Russia to such a highly industrialized country as the United States. Before the depression, fifty per cent of the physicians in the United States had a net income of \$3,500 a year or less; twenty-five per cent had incomes of \$2,500 or less; and eighteen per cent had an income of less than \$1,800 a year. If these amounts were translated into theoretical gold rubles, it would be respectively 7,000, 5,000, and 3,600 rubles, or a monthly income of 600, 420, and 300 rubles. The monthly stipend of physicians in Russia varies from a low average of 180 to 220 rubles up to a maximum of 900 rubles a month for the so-called "big professor." It is true that owing to the paucity of doctors, many of them work a double shift and of course double their earning capacity. The Russian physician, however, participates in so many indirect forms of income by reason of his being able to buy at the closed cooperative stores, and to participate in the general rental percentage of three per cent of the individual's income for rent, that his real income is probably in excess of the theoretical ruble value. It is my impression, however, that the physician earning \$2,500 a year in American money in the United States today is enjoying a higher standard of living than almost any of the doctors in Soviet Russia.

Newsholme and Kingsbury, in discussing the same subject, come to the conclusion that it is doubtful if the earnings of many Russian doctors have a purchasing power lower than \$1,500. The ordinary physician in Russia has considerable spending power, a condition that is shared with the laborer in that many of the fees charged for living are determined largely upon the individual's monthly income, such as one per cent for income tax, two per cent for trade unions and social insurance, and three per cent for rent. Bread, butter, cheese, eggs, meat, coffee, tea, and sugar are still high in Soviet Russia. While the quantity of these commodities may vary as well as the quality, there has been very little tendency in the closed cooperatives for the prices to be raised. The only millionaires, so to speak, in Soviet Russia, are the playwrights, authors, movie directors, and composers who on a royalty basis can receive an annual income as high in some cases as 100,000 rubles.

One must not forget that in the completely socialized medical set-up in Russia one of the most active agents making for its success is the complete police power of the government. Since private practice is non-existent, since there is no choice of physician and all medical practice is free, the sick individual must go to a point of medical consultation or a clinic. The effect of all these factors on venereal disease has been as remarkable as it has been successful. There are venereal dispensaries in all districts. The registration is one hundred per cent complete. There is no social stigma attached to the individual by being afflicted with a venereal disease. Every fresh case is traced, and the contacts are controlled. Before the Revolution there were in Moscow one hundred and sixty-seven fresh cases per ten thousand of the population, and this was

at a time when there was very incomplete venereal registration. In 1927 there were proportionately fifty-seven and three-quarters per ten thousand, and in 1931 thirty-one per ten thousand. Congenital lues in Moscow has fallen from six per cent in 1923 to one per cent in 1930.

Today every man and woman in Russia twenty years of age began his career under a new social order, without any previous knowledge of religion; every individual over thirty owes his present social and economic position, as well as the continuation of that position to the present regime; while for those over forty, who lost all previous standing, position, and income, a new regime is substituted for a former type of living that remains to them only in memory.

The philosophy of the Revolution was a destruction of Czarism, of capitalism, and of religion. Lenin is given credit for the original Marxian quotation that "religion is opium for the people." Out of nine hundred and eighty churches in Moscow that existed before the Revolution only fifty-six remain. It is only fair, however, to say that many of these were destroyed under the exigencies of traffic demands, and not primarily for atheistic reasons. Some of the churches have been converted into anti-religious museums, where the historical pageant of religious development is ridiculed by parallel exhibits supposed to be a pictorial presentation of the Darwinian theory.

History will record the rise of the Bolsheviki to power in Russia as an epoch in human affairs. Yet this tremendous revolution in world affairs is not without its antecedent example. On September 20th, 1792, France declared herself a Republic, and there was fought the Battle of Valmy, which according to Creasey was one of the decisive battles of the world. It is rather significant that, whereas the terror of the French Revolution started from the attempted invasion of France, the terror in Russia started at the cessation of any attempts at invasion of Russia proper.

Lincoln Steffens in 1919 made the statement regarding Soviet Russia, "I have seen the future and it works." It is alleged that Karl Marx stated that his chief diversion in life was to subject everything to doubt, and Lord Balfour ironically alluded to Chicherin that the Soviet formula was "an excellent means of making rich men poor, but a dubious means of making poor men rich." Perhaps the most far seeing statement in regard to the present social plan in Russia is that of Friedman ("Russia in Transition," p. 406): "In life as in a railroad journey, it is important not only to arrive at one's destination, but to enjoy the trip." The same Author further states that the argument put forth by some Soviet sympathizers that there are many defects in the capitalistic system is quite beside the point. It is admitted that there are defects in the capitalistic system, but these do not justify the Soviet organization, for they are suffering from still greater evils. "The Soviet system is designed for the masses. Capitalistic society is designed to raise individual talents to superior levels. The Soviet society is designed to prevent the inferior from falling to greater depths."

One day as my visit to Moscow was drawing to a close, I had a long chat with one of the original Revolutionaries. This gentleman, whom we will call "X," has lived some years in America, and is familiar with American history and American ideology. I said to



him, "X, the Soviet government has taken over all of the economic details of a capitalistic state, namely, the differential wage scheme, the income tax, the sales tax, and so forth. Is not this a trend toward state controlled capitalism?"

"No," he replied, "this is a socialistic state on the way to communism." "What then is the ultimate condition of the people under communism?" He replied, "We will all fare the same, be the same, at all times, at all places. To each shall be given according to his needs. Competition will be eliminated, and by planned economy and planned distribution everybody will enjoy as full a measure of happiness as possible." I said, "X, this is heaven you are describing." Whereupon he turned and indignantly said, "There is no such

thing as heaven; there is such a condition as communism."

In conclusion, upon the variance of human nature and the unexplained biological mutation of personality will come the disruptive factors, for not everybody can be at one and the same time always the same and always happy.

#### REFERENCES

1. Soviet Russia: A Living Record and a History. William Henry Chamberlin. Little, Brown and Co., 1931.
2. Protection of Women and Children in Soviet Russia. Alice Withrow Field. Victor Gollancz, Ltd., 1932, London.
3. Red Virtue. Ella Winter. Victor Gollancz, Ltd., 1933.
4. Red Medicine: Socialized Health in Soviet Russia. Sir Arthur Newsholme and John A. Kingsbury. Doubleday, Doran and Company, Inc., 1933.
5. Russia in Transition. A Business Man's Appraisal. Elisha M. Friedman. Viking Press, 1932.

## The Fifteenth International Physiological Congress, Leningrad and Moscow, August 8-18, 1935

By

A. C. IVY, M.D.\*  
CHICAGO, ILLINOIS

THE memorable feature of previous international congresses has been the scientific program and the pleasure and profit of meeting and discussing matters of mutual interest with foreign colleagues in the international atmosphere of Science. The Fifteenth "International Physiological Congress" not only was memorable in this regard but also in that the large majority of delegates was visiting a country concerning which they had read much and of which they knew nothing by first-hand experience. You may imagine the surprise of some of us, who had carried dried fruit, chocolate, etc., into Russia, when confronted at the opening informal reception (August 8, at 20 o'clock,—8:00 P. M.), held in the magnificent marble hall of the Ethnographical Museum, by the most luxurious and extravagant display of food and refreshments that most of us ever had seen. This surprise was only an introduction to the many surprises, opposites, paradoxes and apparent inconsistencies with which we were to meet, all of which may be explained by the engrafting of new social developments on the old culture of the tsaristic regime.

The Congress was formally opened the next morning by Professor Pavlov in the Uritsky Palace, which was originally built for Potemkin, a favorite of Catherine the Great, later the meeting place for the Duma and the Provisional Government of 1917, and now of the local Leningrad Soviet. The Palace recently had been renovated and the beautiful and famous Round Hall was decorated with palms and flowers. (\*Footnote 1).

Academician Professor Pavlov called the Congress to order and gave the opening address, which, in spite of his eighty-six years of age, was delivered with his characteristic physical vigor and perspicacity. After greeting the members of the Congress, he paid tribute to Sechenov (1829-1915), who was the first Russian to deliver his lectures, not from texts, but from data gathered through his own experiments and demonstrations. Professor Pavlov, pointing out the international aspect of Science, made a plea for peace. He said: "I can well understand the greatness of a war for liberty. At the same time, it cannot be denied that war is essentially a beastly method of solving life's difficulties, a method unworthy of the human mind with its immeasurable resources."

The members of the Congress were then welcomed on behalf of the Soviet Government by I. A. Akulov and, on behalf of the Leningrad Soviet, by I. S. Kadatski (Mayor). Professor Karpinski welcomed the Congress on behalf of the Russian Academy of Sciences. The governmental representatives emphasized that physiology was the foundation of the health of the workers, of medicine and animal husbandry and that Science was of, and for, the people.

The keynote of these addresses was the high regard for and the great attention given Science by the workers and the Government. There can be no doubt of this. But, why is there such a dearth of foreign scientific literature in Russia? And, why are not more of the younger Russian scientists "permitted" to study abroad?

The scientific address of the opening plenary session was delivered by Professor W. B. Cannon (United States). By way of introduction to his technical discussion of, "Some Implications of the Evidence for Chemical Transmission of Nerve Impulses," Professor

\*Northwestern University Faculty of Medicine.

Submitted October 5, 1935.

\*Footnote 1. Before entering the building our attention was attracted by a group of workers, because we observed that the women were working and the men sitting near-by smoking. Among other items of interest, we ascertained that this group of workers had been working night and day to complete their work prior to the Congress, and, on completing it ahead of schedule, had been given a large bonus in rubles.





A photograph of Pavlov taken August 8, 1935.

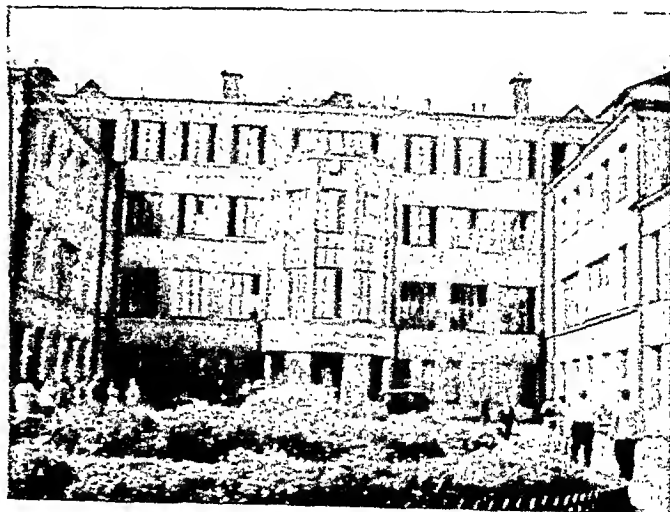
Cannon paid just tribute to Professor Pavlov and briefly discussed international politics as related to Science. (\*Footnote 2). Among other things, he said: "During the past few years how profoundly and unexpectedly the world has changed! Nationalism has become violently intensified until it is tainted with bitter feeling." "Creative investigators of high international reputation have been degraded and subjected to privations." "The scientific triumphs of the past have not been achieved by workers of any single nation; not by representatives of any single racial group." "No other example could illustrate more strikingly the international character of scientific endeavor" than the technical subject Professor Cannon discussed, namely, the "knowledge of the mode of action of autonomic nerves on their effector organs."

Two other plenary sessions were held, one in Leningrad and the other in Moscow. The session in Leningrad was addressed by Professor J. Barcroft (England), the title of his address being, "The Velocities of Certain Physiological Processes," and by Professor L. Orbelli (Russia), the title of his address being, "Pain and its Physiological Effects." The plenary session in Moscow was addressed by Professor L. Lapicque (France), the title of his address being, "Recent Progress in Our Knowledge of Nervous Mechanisms," and by Professor A. Ukhtomsky (Russia), his title being, "Physiological Liability and the Act of Inhibition." The usual boredom of having to sit and listen to an address in a foreign language was avoided at

these plenary sessions. Head phones were available, so that one could make connection with a very competent translator and follow the speaker in anyone of the five official languages of the Congress. This was an innovation in so far as the delegates were concerned, but a necessity for governmental meetings in a country like Russia where so many different languages and dialects are spoken.

All the meetings of the various sections were held in Leningrad. Five sections met simultaneously, some forty sessions being held. About 485 papers were presented. More than 1,200 members and associate members were registered, many of whom were faithful attendants at the scientific meetings. At some of the plenary sessions and entertainments the attendance was 1,500. More than 200 Americans (not all physiologists, of course) were in attendance; there were about 500 Russians.

The arrangements made for the meetings were excellent, when the number in attendance is considered. The special excursions provided by Intourist (the Travel Agency of U. S. S. R.) were superlative. Boats and trains were met in many instances by brass bands. Private cars (Lincolns and Fords) were provided for transfer between hotels and meeting places and, not infrequently, for sight-seeing excursions. The traffic police "knew we were there" and immediately changed traffic to give "right-of-way." Passes were issued which gave free *entré* to busses, street cars, parks, theaters, museums, etc., but purchases could be made only in "Torgsin stores." The evening excursion to Peterhof, the country place and palace originally designed by Peter the Great and completed by Catherine, with its forest, gardens and fountains, illuminated by lights of various colors, was an experience never to be forgotten. The same may be said of the most extravagant banquet tendered by the Organizing Committee and the Leningrad Soviet in "Dietskoye Selo," Catherine's Summer Palace. Set in a scene of great splendor and lasting for four hours, it was followed by an unusual display of fireworks. Also, a splendid concert was given in the State Theater of Drama by many of the prominent Russian artists. In fact, the entertainment was so exceptional that the International



The entrance to a district medical and dental dispensary in Leningrad. Here we saw X-ray apparatus "made in Russia." A dental school was housed in these buildings. All the dental students we saw were women.

\*Footnote 2. International politics has been a prominent item of discussion at every physiological congress held since the World War. Physiologists, like most people, believe in Peace.



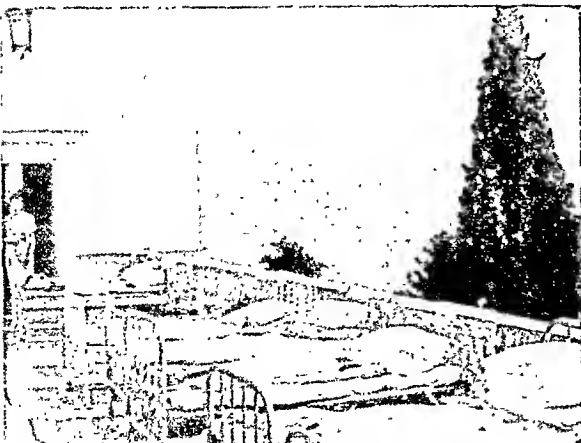
A group of children at a rural communal nursery, with their two nurses. We saw no evidence of "fly consciousness" in Russia.

Committee of Physiologists advised that in the future the entertainment should be so simplified as to be covered approximately by membership fees. (\*Footnote 2).

On the evening of the eighth day, the Congress was moved *en masse* to Moscow where the third plenary session, referred to above, was held in the great hall of the Conservatory of Music, at the conclusion of which the Congress officially was closed. However, that evening a reception and banquet were tendered by V. M. Molotov, Chairman of the Council of the Peoples' Commissars of U. S. S. R., in the Grand Kremlin Palace. This was followed by another concert.

From every aspect, with the possible exception of the dining room services of the hotels, and of the complaints of a few members who contacted insects or had to occupy a sleeping compartment with the sexes mixed, the Fifteenth International Physiological Congress may be viewed as a transcendental success.

\*Footnote 2. It should be mentioned for those who have not visited Russia recently, that the largest palaces in the City are being used as museums and the country places as vacation resorts for the workers. We saw large groups of children and workers being conducted on parties through the museums. The palaces had been recently renovated and had apparently not been molested by the revolutionists.



Livada at Yalta. Formerly the Czar's large summer palace; now, the Rest Home for the Workers at Stalin's Tractor Works.

From the viewpoint of a physiologist, it was a great privilege to visit Pavlov's laboratories in which he and his students have done so much classical work. It was also a privilege to witness the high esteem tendered him by his scientific colleagues and by government officials.

It would appear that Pavlov was the initial stimulus responsible for the remarkable development of physiology, and possibly biology, which has occurred in Russia during the past fifteen years. It is claimed that in Russia there are now 380 institutes working in the field of physiology. In 1917 the Russian Physiological Congress had fifty members. Five hundred Russian physiologists attended the recent Congress.

Part of this mushroom growth undoubtedly has been due to the attention directed by the government to animal husbandry and to the increased production of physicians.

The increase in the number of institutes and research workers has led to a marked increase in the number of articles published. As one listened to, or



Evidence that "the king can do no wrong" even in Russia.

read the abstracts of, the papers presented by the younger Russian biologists, or read the completed works of the institutes, he was impressed by the imagination and enthusiasm of their Authors. On the other hand, it may be said, in the spirit of scientific friendliness, that one too frequently is surprised by the lack of breadth of training, adequate "controls" and critical thought. Many felt that due to the rapid growth there was a deficiency in critical judgment and a need for rigorous criticism and a higher standard of scientific accuracy. When, as a small group, some of us visited a dispensary or some similar institution, we were met not by a single official but by three or more officials, giving us the distinct impression that the "chief" official was apprehensive lest he might be reported for telling us something that he did not say. Taking these and similar impressions into consideration, one wonders whether in such an environment rigorous and stern criticism, marked differences in viewpoint and true scientific freedom are not suppressed. Yet, having met numerous Russian physiologists, having noted the changes already made by the Soviet Government in their system and being assured that further changes will come when practically expedient, I view the future



A view of two buildings in the Metschnikoff Hospital group just outside Leningrad.

of physiological science in Russia optimistically. (\*Footnote 4).

Some of us visited hospitals, dispensaries, nurseries, and prophylactoria, (\*Footnote 5), in an attempt to obtain an insight of the Russian system of medical practice. We learned that, on paper at least, they have a "perfect" system of socialized medicine. In so far as I could ascertain the facts, their system is most analogous to the Swedish system. One finds individual differences of opinion among physicians and patients in regard to how they like the system. Foreign tourists also react differently to the system of state capitalism in Russia, some entering Russia "pink" and returning "red" and others "white."

If one attempts to maintain an emotional balance and evaluate one's responses according to one's past conditioning and that of the Russians, (*i.e.* objectively, which is very difficult) he sees many things that are good and other things that are bad. Thus, when such a person is asked, "how do you like," or, "what do you think of Russia" (after 10 days of it—much too long for many people!), he may reply: "A very interesting experiment is being conducted in Russia. It is to be hoped that it will not be interfered with by external forces and that the Russian experimenters will not interfere with governmental and social experiments going on elsewhere."

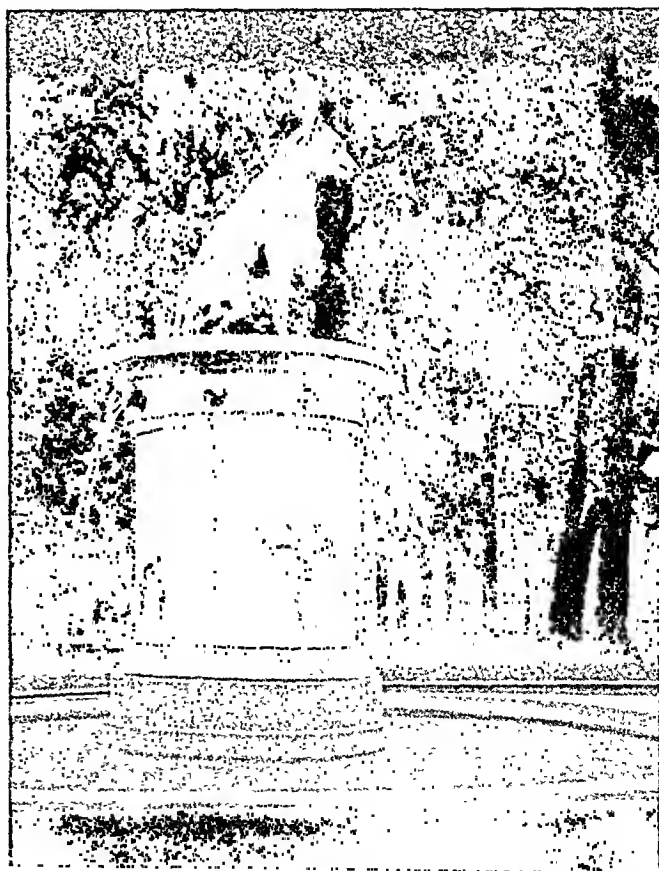
The Russian experiment is in progress, and one cannot pass judgment, except on the basis of theory,

\*Footnote 4. Various sorts of devices, prizes, bonuses, badges, etc., are used to stimulate individual effort among scientists, officials and workers.

\*Footnote 5. A "prophylactorium" is an institution for the "cure" of prostitutes, or, as the Russian officials say, for their "reconditioning." Hard labor is one of the "cures." The following amusing conversation occurred during one of these visits. Noting that the majority of women gave the appearance of being "feeble-minded," we inquired for the percentage of cures. The reply was, "100 per cent." We manifested incredulity, and inquired how many of the women came back. The reply was that a number of them was brought back, but they were "crossed-off," because they had not been cured in the first place.

on an experiment in progress. One may say that a certain part of the technique of the experimenter is good or bad, but the critic who does not know all the details expedient for particular situations may be wrong. In another generation or two, the experiment should be about concluded. Then, and then only, may one pass judgment on its success. At least the prominent Russian experimenters are sincerely idealistic, though they claim to be materialistic, and are not becoming privately rich through graft. The experimenters, however, are well paid and have a high standard of living; this can hardly be said of the mass of workers at present, when their standard of living is compared with that of the mass of American workers.

In other words, from the viewpoint of an experimentalist, the Russians are conducting an interesting experiment, but it is preferable in this experiment to play the rôle of a prominent official, scientist or engineer. The result of the experiment may prove that communism or that state capitalism (not a "dictatorship of the proletariat," which is most repulsive to a thoroughbred American, though it may be expedient in present-day Russia) is not a Utopian dream, but is a practical social procedure.



The Memorial to the Unknown Dog, located in the yard of Pavlov's Institute.

# ABSTRACTS

DUFF, G. L.

*Experimental Cholesterol Arteriosclerosis and its Relation to Human Arteriosclerosis. Arch. of Pathology, 20-1, p. 81, July-Aug., 1935.*

The author gives a detailed and logical review of the literature and the experimental data concerning experimental cholesterol arteriosclerosis, and from a study of the known factors of human arteriosclerosis he attempts to analyze its relationship to the latter. In a brief review such as this it is possible to set forth only some of the more important points of the problem.

The experimental reproduction of human arteriosclerosis in animals has not as yet proved possible. Intimal changes from cholesterol feedings in rabbits is the nearest approach to it. It is not known whether the lipoids play the major role in human arteriosclerosis or not. They may represent either cause or effect. Aside from a few positive experiments in guinea pigs similar lesions have never been produced in other experimental animals than the rabbit. The lesions in experimental animals appear first in the aorta, but only after the liver, spleen, bone marrow and supra-renal glands have become loaded with lipoids. Early lesions in the media have been described by Bailey and by Duff as areas of focal necrosis which later become infiltrated with lipoids. The so-called "foam cells," macrophages, seemingly mononuclear phagocytes, make their appearance only after the destruction of the internal elastic lamina. The initial precipitation of cholesterol takes place within the ground substance of the walls, particularly of the intima. A high cholesterol-emia of some degree is apparently necessary for the development of experimental arteriosclerosis in the rabbit, although an excessive degree is not necessary. A blood cholesterol in rabbits of 2584 mg. per c.c. of blood has been recorded. The usual degree of hypercholesteremia, however, need not be great. Hypercholesteremia has frequently been noted without the production of experimental lesions, making it necessary to assume the presence of other factors in the etiology of such lesions. There is some suggestive evidence of an effect from high protein diets, but no definite proof. There is no evidence of a relationship between hypertension and the production of these lesions.

As regards the influence of the endocrine systems, one fact seems to stand out as of importance. Thyroidectomy seems to hasten arteriosclerotic changes; 696

the feeding of thyroid extract seems to retard them. Potassium iodide retards arteriosclerotic changes, but thyroidectomy abolishes this protection. Local injury to the arteries seems to be of definite importance—trauma, cauterization, epinephrine, nicotine, viosterol and infection all apparently intensify the deposit of lipoids in the injured areas.

The author concludes that some form of injury to the vessel wall is the essential factor which operates in conjunction with hypercholesteremia in the production of experimental cholesterol arteriosclerosis in the rabbit.

The imbibition theory of causation as suggested by Virchow and supported later by Aschoff, Anitschkow, and others, postulates that the lipoids do not arise from degeneration of the arterial wall but that they infiltrate it from the blood stream. The wall is assumed to be normal in structure before the entrance of lipid substances. The subsequent proliferation in the intima is due to the precipitated cholesterol and its esters. Rosenthal adds to this theory the supposition that the elastic recoil of the internal elastic membrane expresses the lipoids and tends to prevent their deposition, thus explaining the absence of arteriosclerosis in the muscular arteries as compared to its prevalence in the larger vessels in which this membrane is more poorly developed. The author holds this conception of Rosenthal's as impossible. In the presence of hypercholesteremia and an associated hyperlipemia, the author necessitates the presence of local precipitating conditions which, operating together with the former, permit the deposit of cholesterol and the histologic changes following in its wake. His reasons for this postulation are: hypercholesteremia does not produce experimental cholesterol arteriosclerosis of itself; injuries to the vessel walls localize and initiate the deposition of cholesterol; experimental cholesterol arteriosclerosis is a patchy process, not a diffuse one; local injuries in the media are known to precede cholesterol deposition in certain instances; the vaso vasorum are known to play a great or greater a role in the distribution and deposition of dyes, as trypan blue, and, by analogy, the precipitation of cholesterol might follow the same channels. Beyond this point the development of experimental cholesterol arteriosclerosis is not capable of accurate analysis.

The author then considers in detail the known factors of human arteriosclerosis and attempts to correlate the data concerning experimental chole-

sterol arteriosclerosis with them. The three main factors recognized in the etiology of experimental cholesterol arteriosclerosis, namely, cholesterol in the diet, hypercholesteremia, and injury to the arteries, are considered as regards their possible significance in the etiology of human arteriosclerosis. The following assertions in brief are made: the result of cholesterol feeding in rabbits does not constitute a valid reason for believing that an excess of cholesterol in the diet plays any role in the etiology of arteriosclerosis in man. Hypercholesteremia is not found with any regularity in association with human arteriosclerosis; it cannot of itself be regarded as a cause of human arteriosclerosis. The initial stage in the development of human arteriosclerosis consists of local changes in the walls of the arteries themselves, changes which are responsible for the subsequent precipitation of lipoids in the affected areas. Thus far the cause of injury to the arteries is unknown.

Noble Wiley Jones, Portland.

RANKIN, FRED W.

*Cancer of the Colon. Notes on its Surgical Treatment. S. G. and O., Vol. LIX, No. 3, pp. 410-414, Sept., 1934.*

The Author discusses the surgical treatment of cancer of the colon as divided into three phases; namely, the one of preliminary preparation, operative, and convalescent periods. During the period of preliminary preparation the treatment may be epitomized by saying that decompression, hydration, vaccination, and rehabilitation are the measures to be carried out. It is advantageous to attempt to decompress chronically obstructed colons by the employment of mild purgatives and irrigation over a period of from three to six days. Recently blood transfusions have been used routinely by the Author during this period. The routine use of an intraperitoneal vaccine of streptococci and colon bacilli has been found to be very advantageous.

Cases showing liver metastases, or with masses fixed to the parietes or to adjacent viscera, are usually inoperable. Certain cases with easily resectable growths, and with small hepatic metastases, should be resected because of the greater comfort it affords the patient. In the Author's experience about 50 per cent. of the cases of cancer of the colon are operable.

The Author believes that graded operative procedures are more advantageous than one stage operations. Cancers of the ascending colon are best

treated by a preliminary end-to-side ileo-colostomy and exploration, followed later by extirpation of the growth and the ascending colon. For growths situated beyond the middle of the transverse colon, and down as far as the junction of the middle and lower thirds of the sigmoid, the Author employs the obstructive type of operation only after complete pre-operative decompression of the bowel. In thin, elderly individuals possessing a carcinoma in a mobile segment of the large bowel, and yet physically unable to stand any extensive operative procedure, the Author employs the Mikulicz operation.

Where neither an obstructive resection, or some type of resection and anastomosis can be done because of insufficient decompression, the Author employs either a caecostomy, or colostomy, as a drainage measure. Caecostomy, after the method of Hendon, employing a Pezzar catheter, is the most satisfactory method.

Primary resection and anastomosis of the left colon, with or without complementary decompression, is rarely indicated in the Author's experience. The dangers of primary anastomosis are great, while the results of graded procedures are relatively safe, and are entirely satisfactory. In the Author's experience the hospital mortality from graded procedures is from five to ten per cent.

N. M. Percy, Chicago.

RIVERS, A. B., STEVENS, G. A., AND KIRKLIN, B. R.

*Diverticula of the Stomach. S. G. and O., Vol. 60, No. 1, pp. 106-113, Jan., 1935.*

The Authors present ten cases of diverticulum of the stomach, and suggest a simple classification of that condition.

1. True diverticula. Those in which the pouch includes all of the coats of the gastric wall without definite evidence that organic disease was the causative factor.

2. Acquired true diverticula. Those in which all the coats of the gastric wall are present although there may be some thinning, and there is evidence that some disease was instrumental in producing the pouching.

(a) Pulsion type of diverticula result from intra gastric pressure which is probably localized.

(b) Traction type of diverticula are incidental to extragastric adhesions.

3. False diverticula or diverticular formations. In these there is a break in the gastric wall resulting from disease.

The etiology of true diverticula is unknown. It seems that the weight of evidence favors a congenital basis for that group of diverticula. Acquired true diverticula usually result from the pull of adhesions to the gall bladder, spleen, pancreas or other adjacent viscera. Acquired false diverticula re-

sult from weakness of the stomach wall produced by inflammation, ulceration, or by neoplasm.

Of the cases presented 10 were removed at operation, while 4 were secured during routine post mortem examinations. The ages of the individuals (cases) ranged from 25 to 59 years; the average age was 42 years. Six of the patients were males; 8 were females. Six of the diverticula were found adjacent to the pylorus, 6 at the cardia, and 2 were some distance from the pylorus on the posterior wall. The diverticula varied from 1 to 7.5 centimeters in diameter. In two cases peptic ulcers were found adjacent to the diverticula; in one an adenomyoma in the diverticulum, and in another a sarcoma in the wall of the diverticulum. In one case a diverticulum was found in the duodenum also; in another multiple diverticula of the colon was found. In 10 of the cases the symptoms of which the patients complained could not be attributed to the diverticulum. The diagnosis of gastric diverticulum cannot be made without roentgenograms; roentgenologic diagnosis is difficult.

The treatment of diverticula of the stomach is, in the main, surgical. The particular surgical procedure in a given case will be determined by the size and location of the pouch, the presence or absence of associated pathology, and the symptoms which it might have produced.

Fourteen cases are reported in detail. Nine figures and a bibliography accompany the article.

N. M. Percy, Chicago.

KOSTER, HARRY, M.D., AND KASMAN, LEWIS T., M.D.

*Acute Pancreatitis. Arch. Surg., Vol. 29, No. 6, pp. 1014-1024, Dec., 1934.*

This article is a general discussion of this disease and a report of 22 cases treated by the Author.

In this series of 22 cases, 5 cases were correctly diagnosed preoperatively and the disease was suspected in three others. The age incidence varied from 17 to 78 years of age, 63.64 per cent of the group were less than 35. The average age incidence was 35.27 years. 36.36 per cent were men and 63.64 were women.

A history of biliary tract disease was present in 63.64 per cent of the cases.

The duration of the present illness in this series varied from 1 day to 2 weeks. In 40 per cent of the cases, it was 24 hours or less in 63 per cent of the cases, there was a sudden onset of pain in the epigastrium or right upper quadrant or both, followed by vomiting. In the remainder of this group, the onset was less precipitous but similar. Shock and cyanosis were present in 31

per cent. Transient glycosuria was present in 2 cases.

Those cases not diagnosed as acute pancreatitis suggested a variety of conditions, acute cholecystitis (63 per cent), perforated gastric ulcers (14 per cent), acute obstruction of the common bile duct (22 per cent).

At operation, the pancreas showed the typical inflammatory changes in all cases, fatty necrosis of the omentum and the typical sero-sanguinous exudate was observed in 63 per cent of the cases. In 50 per cent a greenish discoloration of the fat in the gastro-hepatic omentum, characteristic of this disease was noted. In only 18 per cent of the cases, was the pancreas the only organ in which there was apparent involvement. Cholecystitis with concomitant cholelithiasis was present in 54 per cent of the cases. Cholecystitis alone was present in 18 per cent, and common duct stones alone were found in 9 per cent of the cases.

The prevalent opinion that acute pancreatitis is usually secondary to an involvement of the biliary tract as the result of which there may occur an intrapancreatic activation of trypsinogen and a subsequent autodigestion of the gland seems to be borne out by this group of cases.

The diagnosis of acute pancreatitis is not difficult when an onset is presented of knifelike pain in the epigastrium associated with prostration and cyanosis. This pain is usually similar to that of a perforated gastric ulcer and a careful past history is, therefore, very important. In cases where the onset is less precipitous, where symptoms are present suggesting an exacerbation of inflammation of the biliary tract, acute pancreatitis should be suspected. This is particularly important when the patient is a male, because acute pancreatitis is as frequent in males as in females in contradiction to the higher incidence of disease of the biliary tract in the latter.

The mortality in several series of cases reported since 1910 is given. This varies from 68 per cent to the Author's series which is reported in the present article as 22.7 per cent. Early operation is the most important single factor in further reducing this operative mortality.

The surgical treatment of acute hemorrhagic pancreatic inflammation should include the following steps: Drainage of the biliary tract, removal of the gall bladder, if it is diseased or contains stones, removal of calculi if present from the common duct, being certain that no stones are left in the region of the head of the pancreas, splitting of the capsule of the pancreas for the relief of edema and drainage of the lesser peritoneal sac and pancreas.

N. W. Swinton, Boston.



## SECTION XII—"The Clinic"

### A Case of Noma (Cancrum Oris) Complicating Non-Specific Ulcerative Colitis

By

JOSEPH S. DIAMOND, M.D.\*  
NEW YORK, NEW YORK

THE extreme rarity of noma in adults, especially in association with non-specific ulcerative colitis, prompts me to report this case. With the exception of instances of noma occurring as complications of dysentery in infants and children and the diarrheas of undernourished and marasmic babies, a careful search of both the recent and older literature fails to reveal any report of the association of noma with ulcerative colitis in adults. In a series of 695 cases of ulcerative colitis collected at the Mayo Clinic over a period of five and one-half years (January 1, 1923, to July 1, 1928) and reported by Bergen (1), there were a total of 278 complications, which varied in nature from local intestinal conditions to arthritis, cutaneous disorders, endocarditis, etc. No mention of the occurrence of noma is made, however. In Logan's (2) series of 117 cases, and in Lynch and Felsen's (3) forty-one cases no mention is made of any oral complications. In Jones' (4) report of seven cases of ulcerative colitis with peripheral complications, two cases are mentioned with ulcerative stomatitis and three cases with ulcer of the cornea, which he attributed to dietary deficiencies and which cleared up with restoration of adequate nutrition. No Vincent's organisms were found in the mouth lesions. Mackie (5) cites the occurrence of glossitis and stomatitis among other nutritional disturbances in ulcerative colitis, and ascribes these to a deficiency state. Glossitis was the most common manifestation in his series. Small aphthous ulcers were found in only

four out of seventy-five cases of ulcerative colitis. He also reports an extension and spreading skin gangrene of the flank, in one case, which occurred suddenly following ileostomy, and which could not be attributed to any known cause. Aerobic and anaerobic cultures were negative. Mackie believes that the factor of deficiency in his series is a secondary manifestation of ulcerative colitis rather than the primary cause of the disease.

#### REPORT OF CASE

Mr. A. G., age 28, married, white, salesman, born in the United States, was referred to the Sydenham Hospital on April 2, 1933, by Dr. I. Margulies. The patient gave the following history: One month before admission, he began to have loose stools which contained some blood. Two weeks after the onset, the diarrhea grew worse, the patient having as many as ten movements a day, accompanied by cramp-like pains in the lower abdomen. There was a slight elevation of temperature (101 degrees) with occasional vomiting. Appetite was diminished. The patient lost weight and became weak. He remained in bed for two weeks and then entered the hospital.

Upon admission, the patient appeared well developed although somewhat pale and dehydrated. Pulse was rapid (120) and small; abdomen somewhat distended and tenderness in both flanks. Proctoscopic examination revealed the presence of bleeding ulcers of varying sizes, extending from the upper part of the rectum upwards into the sigmoid. Blood picture: hemoglobin 65%; red blood cells 4,340,000; white blood cells 21,400. Differential count: 75% polymorphonuclear neutrophils with 18% segmented and 57% band forms, 11% lymphocytes, 12% monocytes, and 2% eosinophiles, with a few myelocytes and metamyelocytes, and occasional Türk cells. Some leucocytes showed vacuoli-

zation. The urine was negative. Feces were foul smelling, loose, dark brown in color and mixed with blood. Blood agglutination for typhoid, paratyphoid A and B was negative. The Felix-Weil reaction was negative. Wassermann and Kahn tests were negative. Bacteriological study of the feces showed colon bacilli, streptococcus fecalis, diplococci, atypical dysentery bacilli of Flexner. Stool was negative for amoeba, parasites, and monilia.

Glucose and saline infusions were given and the patient was placed on a balanced, low-residue diet. Daily rectal irrigations with non-irritating fluids such as physiological saline and chamomile tea, and mild antiseptics such as neutral acriflavine (1:5,000) were used at different times. Kaolin, bismuth and opiates were administered per os to control the frequency of the movements. Due to the inability to obtain a pure strain from the base of an ulcer, a mixed vaccine was prepared consisting of streptococci, diplococci and colon bacilli and was administered in increasing doses.

During the first five days the temperature fluctuated between 100 degrees and 102.5 degrees (F). Pulse continued rapid and small and persisted at 120 and over. On the fifth day the temperature rose to 104. The patient appeared very toxic, and became disoriented, elated and restless. The picture resembled a mild manic psychosis. Paraldehyde was given and the condition cleared up within a few hours. Blood cultures made at this time were negative after seventy-two hours. A blood transfusion was given with slight general improvement.

Bowel movements seemed somewhat controlled; nutrition was maintained; but the pulse rate remained unaltered and the temperature persisted ranging from 99 to 103.4 degrees. The white blood count remained elevated reaching as high as 25,000-28,000, always with a persistently high percentage of band forms (as high as 60%). On April 13,

\*Attending Gastroenterologist Sydenham Hospital, New York, New York.  
Submitted August 27, 1935.



the patient again showed slight disorientation and had incontinence of feces. This cleared up in a very short time.

On April 14, the patient complained of pain in the teeth of the left upper jaw. Examination revealed a small grayish-white ulceration about two to three millimeters in diameter. This ulcerative process increased in size daily. Radiography showed normal second and third molar teeth. Within four days, the ulceration quickly spread from the gingiva over the inner side of the left cheek over an area of about three centimeters in diameter. The lesion began to assume a dark-grayish appearance and developed a strong fetid odor. A smear from the wound, made at this time (April 18), revealed the presence of fusiform bacilli and spirochetes; culture revealed streptococci and staphylococci. Noma was promptly suspected. The leucocyte count began to drop daily, falling to 16,000, 10,000, and on April 17, was 8,500, with 13% polymorphonuclears and 46% band forms. The possibility of an agranulocystic picture was considered. On subsequent examinations, however, the leucocyte count was found to be rising and fluctuated between 12,000 and slightly over 20,000. Local applications of a suspension of neosalvarsan in glycerin were made several times a day. The mouth was also irrigated with solutions of sodium perborate. A blood transfusion was again given. The condition of the mouth was not influenced by the salvarsan and the ulceration continued to spread.

On April 19, the patient suddenly developed a marked parotitis on the left side, with pain and tenderness. About two days later, the right parotid gland became similarly swollen. A sense of deep fluctuation was felt in both glands and incision and drainage were considered, but within the next few days the swelling of the glands receded spontaneously and both glands returned to normal.

On April 22, the patient had several copious intestinal hemorrhages, the first one during the night, about 400 c.c. and again later, about 500 c.c. of bright red blood. The pulse rose to 150-160. Transfusion was promptly given, along with thromboplastin and calcium gluconate. The hemorrhages ceased and the patient rallied. The pulse rate decreased to its previous value for several hours. On April 24, he was again incoherent and fingering the bedclothes. The blood showed a bleeding time of eight and one-half minutes; clotting time was three minutes; and blood platelets were 200,000.

On April 25, the gangrenous ulceration in the mouth suddenly spread to the hard palate, covering more than half and reaching as far back as the soft palate, spreading simultaneously over the entire inner part of the left cheek, and causing a marked indura-



Fig. 1. Noma showing gangrene involving roof of mouth and induration and edema of lip and left cheek (just before perforation).

tion of the cheek and edema of the upper lip (Fig. 1). A sharp line of demarcation was seen at the margin of the ulcerating process. The odor was very foul, penetrating throughout the room. Alimentation became somewhat difficult, but the patient was cooperative and made every effort to consume the liquid and soft foods given to him.

At this time ultra-violet radiation was instituted, and local treatment to the gangrenous portion of the mouth made with the Kromayer lamp. No improvement was noted. The gangrene spread, involving the entire palate and inside of the cheek. An attempt was made to stay the process by removal of the necrotic tissue. The sloughs were removed daily to encourage drainage and expose healthy tissue wherever possible.

Another blood culture was negative after seventy-two hours. Cultures from the mouth were positive for non-hemolytic streptococci and staphylococcus citreus. B. Fusiformis and spirilla, at this time, were no longer found on the surface of the gangrenous tissue, but could be found in the deeper strata after removal of the slough.

The hemoglobin dropped to 55% and the red blood count to 3,890,000. Blood transfusion was again given on the 28th of April.

On May 30 and May 1, the patient was again irrational and had incontinence of urine and feces. The mouth was irrigated with a 1:5000 solution of potassium permanganate and an "Enzymol" plug was introduced. The red cell count fell to less than three million and the hemoglobin to less than 55%. Another transfusion was given on the 4th of May. There was very marked edema of the lips and upper eyelids. The patient also developed a moderate degree of exophthalmos of the left eye. The center of the left cheek became dark. On May 5, a radical operation was undertaken to remove the slough with the high frequency cautery, cutting into the bordering healthy

tissue. Following another transfusion the entire soft structure of the left upper maxillary region was also removed exposing the bone. The hard palate also was exposed. The slough of the soft structure of the left cheek and buccal mucosa was excised. The center of the left cheek was about to perforate.

On May 6, the cheek had perforated and the patient was failing rapidly. He became stuporous and incontinent and in spite of stimulation, intravenous glucose, etc., he died on the following day, May 7.

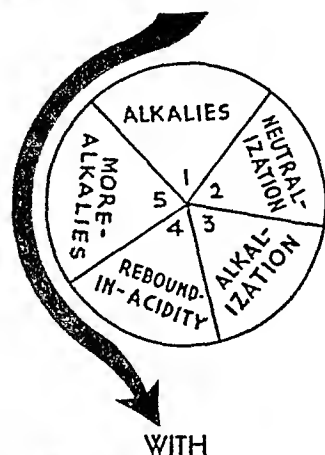
## DISCUSSION

In the early part of the Seventeenth century Bathus (6) described for the first time the symptom complex of noma, although the word "noma" has been employed since the time of Hippocrates to denote destructive and perforating lesions. Van der Voerde (6), in the latter part of the Seventeenth century, applied the term to this clinical picture. Other names that have been employed are "cancrum oris," "cancer acuticus," etc., and due to its high mortality, which reaches from seventy to eighty per cent, it has also been called "malum mortum."

## ETIOLOGY

The causation of noma has been attributed to many factors. The nutritional element, both general and local, was considered the sole cause by the older writers. Martin (7), in 1796, and others such as Marshall Hall (7) and Karl Weil (8) (1916) stressed the association of malnutrition and noma from their observation that noma, as a complication of the exanthemata, is more frequent among undernourished and debilitated children. Henoch (9) called the disease "cachexia pauperium"

## Avoid the Vicious Circle of Alkali Neutralization



WITH

# TRI-CALSATE

• Unlike the alkaline antacids (sodium bicarbonate, magnesium oxide, etc.) TRI-CALSATE does not stimulate the secretion of gastric HCL.

• Neither does TRI-CALSATE alkalize the stomach contents for it is a *buffered neutral antacid*.

• Yet, TRI-CALSATE is a powerful neutralizer of gastric HCL, palatable and non-irritating.

• That's why extensive clinical experience proves the definite superiority of TRI-CALSATE in the treatment of the gastric hyperacidity syndrome.

Available on prescription or direct in 4 oz. and pound bottles.

Write or send the coupon for complete literature and a trial supply.

**F. H. PAXTON & SONS, Inc.**

Mfg. Pharmaceutical Chemists  
CHICAGO, ILL.

F. H. Paxton & Sons, Inc.  
451 E. Ohio St.  
Chicago, Ill.

Please send me literature and a trial supply of Tri-Calsate.

Name.....

Address.....

City & State.....

and attributed it likewise to the poor living conditions, poor nutrition, and uncleanness, and unhealthy dwellings. It was more commonly encountered in the older institutions where nutrition and hygiene were in

virus was the underlying cause. Bouday (15), however, seems to have definitely established the bacterial origin of the process. He demonstrated *B. fusiformis* and spirilla in the peripheral healthy

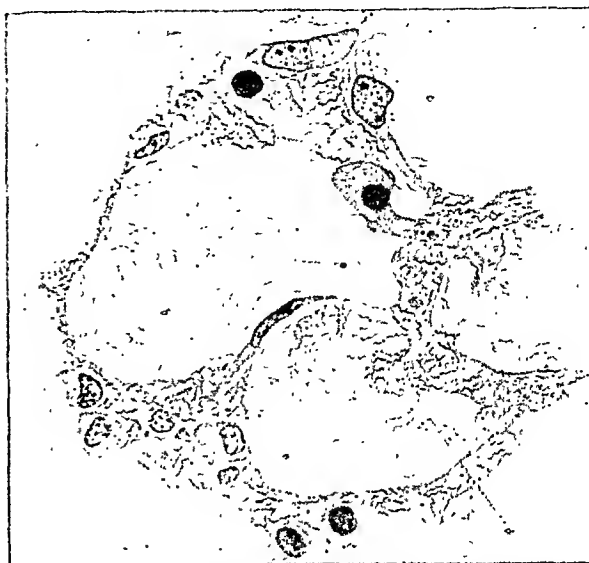


Fig. 2. (After Bouday) Showing pure strain of spirilla and fusiform bacilli extending into healthy tissue. No other form of microorganisms are seen.

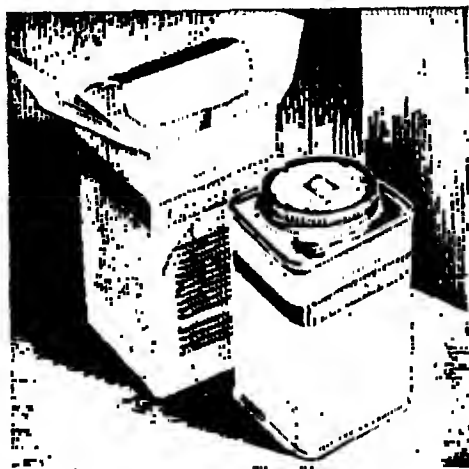
a primitive state, from which it has also received the name "hospital gangrene."

Woronichin (10) held the lesion to be a trophoneurosis which he confirmed by experiments in which the extirpation of the infraorbital nerve of a dog was followed by the appearance of gradually increasing ulceration on the corresponding lip. These, however, were regarded by Waurick (11) and Krassin (12) as decubitus ulcers following trauma to the anesthetized lip. Ziem (12) regards it as an anemic necrosis, following thrombosis of the blood vessels of the mouth. The histological studies fail, however, to reveal thrombi in the larger vessels.

Since the discovery of Plaut (13) and Vincent (14), in 1894 and 1899, of spindle-shaped bacilli and spirilla in inflammatory process of gangrenous character in the mouth and throat, the bacterial causation of noma has assumed primary importance. For a time questions were raised (Baumgarten 6) whether these microorganisms, including streptococci and staphylococci, etc., were not secondary invaders multiplying in necrotic tissue. Others, such as Heinemann (11) and Strada (11) maintained that a filtrable

tissue surrounding the lesion (Fig. 2) removed during the life of the patient. In fact he was able to prognosticate the outcome from the degree of invasion of the healthy tissue, the fewer the bacteria, the better the outlook. Furthermore, he found these two specific microorganisms in the healthy zone to the exclusion of any others, while in the adjacent necrotic tissue, streptococci, staphylococci, thick rods, and other organisms were present. All these findings have been confirmed by Kalina (6) and a large number of investigators such as Bertheim, Grawitz, Elder, Guizetti (16), and others who substantiated the findings pertaining to the symbiosis of the *B. fusiformis* and spirilla in ulcerous and gangrenous stomatitis. That these bacteria are not harmless saprophytes harbored in the mouth, has been demonstrated by Vincent who has proven that they are the causative agents for the inflammatory changes of Vincent's angina, and that in debilitated children with poor nutrition, in chronic diseases, the organisms become more virulent and produce profound gangrenous changes.

It is claimed by Perthes (16), Krahn (16) and Bouday (15) that



# Gastric Hyperacidity

In the relief of gastric hyperacidity, *speed* is essential—Cal-Bis-Ma provides it. The neutralizing effect should be *prolonged* so as to prevent secondary acid rise—again Cal-Bis-Ma takes care of that. The irritated gastric mucosa should be soothed and protected from further irritation—that, too, is an important mission of Cal-Bis-Ma. Send for a trial supply and descriptive literature.

# CAL-BIS-MA

WILLIAM R. WARNER & CO., INC.  
113 WEST 18TH STREET • NEW YORK CITY

Cal-Bis-Ma (powder) is supplied in tins (with removable label) containing  $1\frac{3}{4}$  and 4 ounces and one pound. *Tablets*, in bottles of 110.

the spirillum is the initiator of the necrosis and forces its way into the healthy tissue, as though paving the way for the *B. fusiformis*. This mass invasion of the normal tissue by the spirilla is the first step in the gangrenous process, and complete necrosis can only occur if the *B. fusiformis* find their way into the tissue along with the spirilla. In our own observation, in the case reported, when the gangrene was fully developed the *B. fusiformis* and spirilla could no longer be found on

the surface. Only after the removal of the gangrenous slough could these microorganisms be demonstrated in smears taken from the underlying exposed tissue. Vincent's observations were that where the *B. fusiformis* were found alone, the process was milder without any deep ulceration. These form a crust on the surface which simulates a diphtheritic membrane, and in these pseudomembranes one finds exclusively *B. fusiformis*. The *B. fusiformis* causes inflammation and irritation. The

brownish-green gangrene is due to numerous and various bacilli and cocci which grow on the tissue surface. While the same bacteria are found in Vincent's angina, without the necrotic process present in noma, the histological pictures are identical, differing only in degree, the difference being due to the increased virulence of the organisms and the lowered resistance of the tissue, as in the severe infections where the blood and the blood-forming organs are also attacked.

#### PATHOLOGY

Rona (17) describes three characteristic zones. The first zone is the superficial gangrenous portion which is recognized as a thick diphtheritic membrane. It consists of homogeneous cells without nuclei which, with fibrin and red cells are converted into hyaline-like poorly staining mass. Zone two is beneath the superficial crust and consists of an infiltration with groups of polymorphonuclear leucocytes and growing connective tissue cells. This does not extend very deeply as the infiltrated tissue early undergoes coagulation necrosis. A fibrin boundary can often be seen between the two zones. The walls of the blood vessels in the vicinity of the inflammatory process show very early the appearance of coagulation necrosis. Zone three is the healthy zone. The transition from diseased to healthy tissue is abrupt. The process presents a sudden death of tissue without noteworthy reaction of neighboring tissue.

Bouday (15) also found a sharp line of demarcation between the healthy and necrotic tissue. At the periphery, the tissue still stained fairly well and the fat connective tissue and muscle cells were still recognizable; while in the brownish-green, gangrenous area, the tissue was disorganized, no definite cellular structure being discernible, the spaces were filled with clumps of pigment. The blood vessels were thrombosed. In the peripheral healthy zone, there was neither hyperemia nor thrombosis of the vessels. However, the *B. fusiformis* and spirilla, as previously mentioned, were seen forcing their way into the adjacent tissue, while in the necrotic zone, there were masses of fusiform and strand-like organisms which strained with fuchsin, and in the superficial brownish-green gangrenous tissue, many cocci and clumps of small

## For "INTESTINAL TOXEMIA"

## KARICIN

*The combined adsorptive-detoxifying effects of kaolin and ricinoleate aid in*  
Detoxifying intestinal bacterial toxins

Checking fermentation

Reducing flatus

Soothing irritated mucosa

Establishing normal bowel action

An average tablespoonful of Karicin contains:

|                            |             |
|----------------------------|-------------|
| Pure Colloidal Kaolin      | 53 grs.     |
| Ricinoleate                | 6 grs.      |
| High Viscosity Mineral Oil | 1 1/4 drams |

The new flavor insures a new palatability  
—the same detoxifying properties.

*Send for a clinical sample and literature.*

**THE WM. S. MERREL COMPANY**  
CINCINNATI, U. S. A.

# The NORMAL STIMULATION TO COLON PERISTALSIS ....*Distention*



*The ideal therapeutic agent* for correcting constipation by physiologic distention should satisfy these requirements:

1. It must be non-irritating to the sensitive gastro-intestinal tract.
2. It must supply bland bulk to a spasmodic colon to overcome cramping.
3. It must lubricate the bowel, to facilitate passage of the gastro-intestinal content.
4. It should not interfere with digestion and, preferably should not be digestible, itself.
5. It should have a viscous tenacity, in order to unite the fragmented stools during the diarrheal stage.
6. It should not leak from the anus when taken in quantities sufficient to afford the desired therapeutic effects.

## MUCILOSE

*Complies Fully with All These Requirements*

This hemicellulose is obtained from the *Plantago loeflingii*. Supplies bland, non-irritating bulk. Mucilose does not leak — does not impair digestion.

*Effective . . . Easy to Take . . . Economical*

Mucilose offers a non-irritating stimulant to the spastic colon, by physiologic distention.

### FREDERICK STEARNS & COMPANY

DETROIT NEW YORK KANSAS CITY SAN FRANCISCO  
WINDSOR, CANADA SYDNEY, AUSTRALIA

FREDERICK STEARNS & COMPANY

Detroit, Michigan

Dept. D. D. 1

Please send me a supply of Mucilose for clinical test.

Dr. ....

Address. ....

City. .... State. ....

thick bacilli were found. Bouday claims that the absence of *B. fusiformis* and spirilla in vital tissue is a good prognostic sign.

### TREATMENT

The treatment of noma is still very unsatisfactory as can be seen from the high rate of mortality. Many forms of therapy have been advocated each one claiming some measure of success.

The most important is early surgical excision which is best carried out

today with the electro-cautery, extending the incision into the surrounding healthy tissue. Curettage of the slough is also recommended. Golianitzky (18) also advocates incision and drainage of the ducts of the salivary glands (parotid and submaxillary), producing external fistulae, since he believes the lesion is spread by the infected salivary secretion.

Petrusehy (19) claims to have been successful in a few instances

with the use of anti-diphtheria serum, where the Loeffler's bacilli have been found in abundant numbers in the ash-gray superficial membrane.

In view of the presence of the spirilla, the use of salvarsan has been advocated both locally and intravenously. Romeo (11) reports the cure of four cases with this treatment. Plaut (11) cured one case. Various forms of radiation therapy have also been employed, such as the red lamp, and X-ray. Locally all forms of mouth antiseptics and deodorants are to be used. Metaphen, potassium permanganate, hydrogen peroxide, perborates, zinc chloride, copper sulphate, etc., and iodoform applied in pledgets have been recommended and also various dyes such as methylene blue, gentian violet, and acriflavine.

In the case reported, removal of the slough was begun early and complete surgical excision with the electro-cautery was done about two weeks after the onset of the process.

The application of a suspension of neosalvarsan in glycerin was employed as a first measure, when the lesion was still small. In spite of its free and early use, the lesion continued to spread.

Radiation therapy was also employed in the form of ultra-violet light, locally, by daily use of the Kromayer lamp. There was also application of the quartz light over the body. No visible impression was made by these procedures. All types of mouth antiseptics were used.

The general condition of the patient must be taken into account. In this instance, the markedly debilitated state from the persistent diarrhea, intestinal hemorrhages, marked toxemia with high and irregular temperature, and high leucocyte count with the large percentage of immature forms, interfered with the success of the treatment in spite of five blood transfusions.

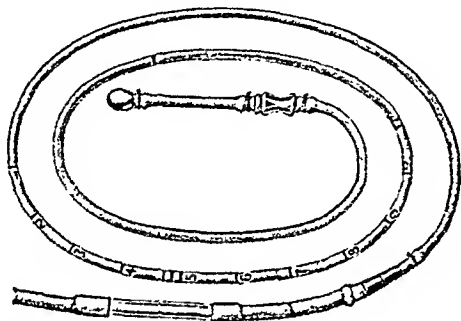
### CONCLUSIONS

1. A rare case of noma in an adult, complicating non-specific ulcerative colitis, is here described, possibly the first one of its kind to be reported.

2. The *Bacillus fusiformis* and the spirillum were found very early on the surface of the lesion, but with the development of the gangrene, could be recovered only from the depths of the lesion, after removal

## DR. TWISS' DUODENAL TUBE

Designed by Dr. John Russell Twiss, New York City



**A** RADICALLY new tube with bucket and terminal swivel weight that guides tube and bucket easily through pylorus into duodenum without kinking or curling.

The use of slightly larger and more resilient tubing tends to prevent looping in stomach.

The small diameter of solid terminal tip makes engagement in pylorus easier and the smaller size tubing attached is drawn after it by peristaltic action on the terminal ball. Thus the small size bucket which is attached by the means of swivel connection between terminal ball and bucket permits torsion of terminal ball without affecting duodenal tube and bucket or causing it to loop in the stomach.

Construction of slots in bucket allow free flow of fluid. Concavity prevents adherence to visceral walls. Terminal

ball and bucket are attached to rubber tubing by silk thread, but without use of knots.

The rubber tube has the standard one, two and three ring marking, but in addition the tube is calibrated in inches from the two-ring marking to a point four inches beyond the three-ring mark. This calibration is advantageous where drainage is to be repeated, because the three-ring mark represents only the distance where bile may be obtained in the average patient. Since there is a variation of length required, the correct length may be recorded for reference.

For descriptive folder giving full technical details, usages and advantages, address:



F. SKLAR MANUFACTURING CO.,

BROOKLYN, N. Y.



# The NEW SWEDISH X-RAY GRID

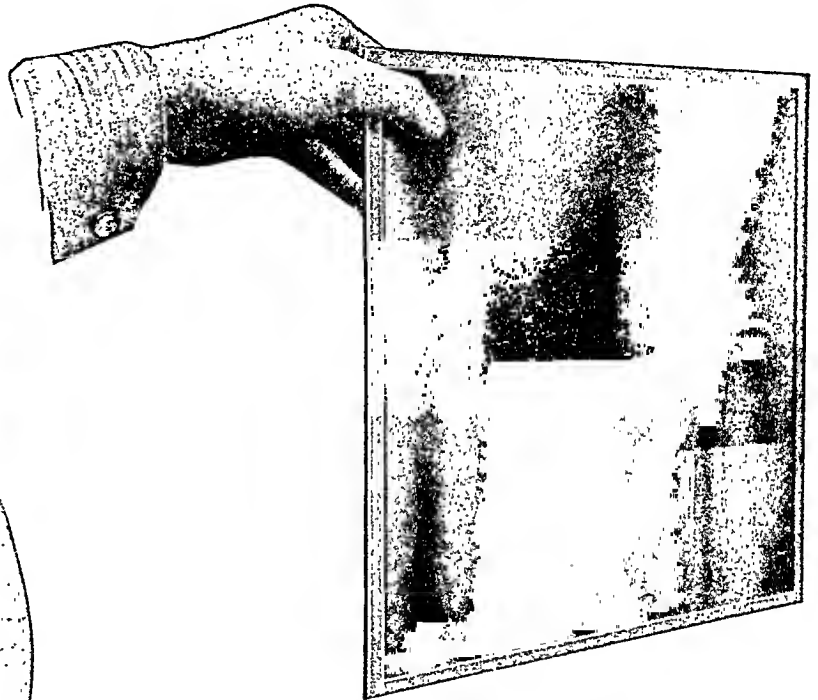
According to Dr. Lysholm, Stockholm-Sweden, is an entirely new type of Bucky Diaphragm for fluoroscopic and radiographic work.

The LYSHOLM GRID is recommended especially for bedside work and for high power fractional second exposures.

The GRID LINES are so fine that they are practically invisible.

CONVINCE YOURSELF of the outstanding features of the grid by availing yourself of the 10 DAYS FREE TRIAL OFFER WITHOUT ANY OBLIGATION TO YOU.

No special Bucky Table necessary. It may be attached to any table or fluoroscope.



Thickness: only 1/8"

Weight: according to size from 6 oz. to 2 1/2 lbs.

|       |                |         |              |          |          |
|-------|----------------|---------|--------------|----------|----------|
| Size: | 5 1/2 x 7 1/2" | 8 x 10" | 12 1/2 x 13" | 13 x 16" | 14 x 17" |
|       | \$35.00        | 60.00   | 90.00        | 100.00   | 110.00   |

ALSO INQUIRE ABOUT OUR UNRIVALLED  
INTENSIFYING SCREENS "SINEGRAN"

**Adlanco X-Ray Corporation**  
54 Lafayette St. New York, N. Y.

Please  
send me



- ☐ more literature on the Lysholm Grid D. D. N. 11  
☐ on 10 days free trial one Grid size.....  
☐ also literature on Intensifying screens SINEGRAN  
 Dr.....  
 Address.....

of the slough. This substantiates Vincent, Bouday and Kalina with regard to the relationship of these organisms to noma as causative agents, and the manner of their spread through the tissue.

3. The marked general toxemia accompanying this fulminant type of ulcerative colitis must be considered as the predisposing factor.

#### REFERENCES

1. Hargen, T. A.: Complications and Sequelae of Ulcerative Colitis. *Ann. Int. Med.*, 3, 335-352, 1929.
2. Logan, A. H.: Chronic Ulcerative Colitis: A Review of 117 Cases. *Northwest Med.*, 18, 1-9, 1919.
3. Lynch, J. M., and Felsen, J.: Non-specific Ulcerative Colitis. *Arch. Int. Med.*, 35, 433-456, 1925.
4. Jones, C. M.: Peripheral Complications of Ulcerative Colitis. *Med. Clin. North Am.*, 16, 919, 1933.
5. Maekie, T. T.: Ulcerative Colitis: II. The factor of deficiency states. *J. A. M. A.*, 104, 175, 1935.
6. Cited from O. G. Kalina: Material zum studium der Noma. *Zeitschr. f. Otolaryng. u. Rhinol.*, 16, 133-150, 1927-28.
7. Cited from Weil (8).
8. Weil, Karl: Noma nach alimentarer Schädigung Inaugural-Dissertation; Strassburg, 1916.
9. Henoch, Eduard: Vorlesungen über Kinderkrankheiten, Berlin, p. 478, 1903.
10. Woronichin, N.: Ueber Noma, nach Beobachtungen in Elisabeth-Kinderspitale während 17 Jahren. *Jahrbuch. f. Kinderh.*, 26, 161, 1887.
11. Wauriek, Walther: Die Eisherigen Ergebnisse der Nomaforsehung Inaugural-Dissertation. Geithain-Leipzig, 1922.
12. Cited from Wauriek.
13. Plaut, H. C.: Studien zur bakteriellen Diagnostik der Diphtherie und der Anginen. *Deutsch. Med. Wchnschr.*, 49, 924, 1894.
14. Vincent, M. H.: Recherches Bactériologiques Sur l'Angine à Bactéries Fusiformes. *Ann. d. l'Inst. Pasteur*, 13, 609, 1899.
15. Bouday, K.: Zur Pathogenese der gangränösen Mund- und Rachenentzündungen. *Beitr. zur Patholog. Anatomie*, 38, 255, 1905.
16. Perthes: Ueber Noma und ihre Erreger. *Munch. Med. Wchnschr.*, 461, 575, 1899.
17. Rona, S.: Zur Aetiologie und Pathogenese der Plaut-Vincentsehen Angina, der Stomatocae, der Stomatitis gangraenosa idiopathica, beziehungsweise der Noma, der Stomatitis mercurialis gangraenosa und der . . . athol-  
Noma, 502, 1460, 1923.
18. Gollanitzki, . . .  
Abstrat . . .  
1460, 1923.
19. Petruschky, J.: Zweiter Fall von Diphtheria-Noma-Noma faciei; Behandlung mit Heilserum. *Deutsch. Med. Wchnschr.*, 24, 600, 1898.

## ABSTRACTS

RICHTER, H. M., M.D., F.A.C.S.

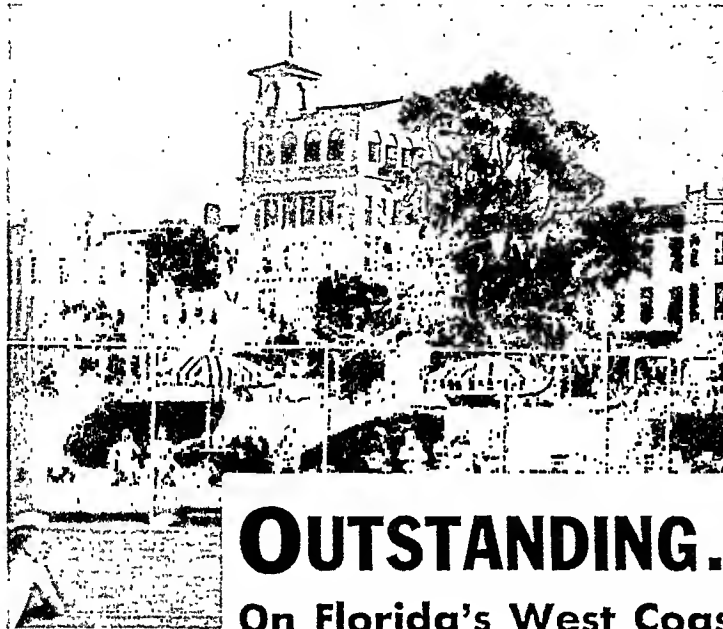
*Gastric Resection for Peptic Ulcer: Technique. S. G. and O., Vol. 59, No. 3, pp. 337-343, Sept., 1934.*

The purpose of this paper is to present the Author's conception of the objective to be obtained in radical subtotal resections of the stomach and to give a short description of the most important points in technique.

Neutralization and reduction of gastric acidity are incidentally obtained following adequate subtotal resection of the stomach and are not the prime objective of resection. The object of gastric resection for benign ulcer is the removal of the ulcer bearing segment of the stomach, which is the lesser curvature and distal half or more of the stomach, and first portion of the duodenum. The poor results following surgery for benign gastric ulcers have been due largely to technical errors and also to a non-realization of the objective to be obtained. He believes that if a resection is to be done at all, it should be a radical resection.

The usual preoperative preparation of these patients is discussed. The regulating of a proper water balance is emphasized. Transfusions are given when indicated, especially in cases which have been hemorrhaging and gastric lavage is freely used where there has been obstruction and dilatation of the stomach. In discussing acute perforations of gastric ulcer, the Author points out that if the patient is operated upon at an early period following the perforation, a radical resection may be done without excessive danger to the patient.

Important points only in the technique as described will be mentioned. The Author follows the Hoffmeister and Finsterer method in doing



## OUTSTANDING..

### On Florida's West Coast

**H**OTEL CHARLOTTE HARBOR is one of Florida's finest and loveliest resort hotels. In a beautiful setting, directly on the water, at Punta Gorda on the West Coast. Own sporty 18 hole golf course, bathing from the hotel, tennis, trap and skeet shooting—wonderful quail shooting and fishing. Unique swimming pool of mineral water for warm healthful bathing.

All rooms face the water and front grounds. Special attention is given to the table and service for which the hotel has long been noted. Select Christian clientele. On Tamiami Trail, 100 miles south of Tampa—Through cars.

Now open. Wire reservations collect or send for booklet to Mr. Floyd Alford, Jr., manager.

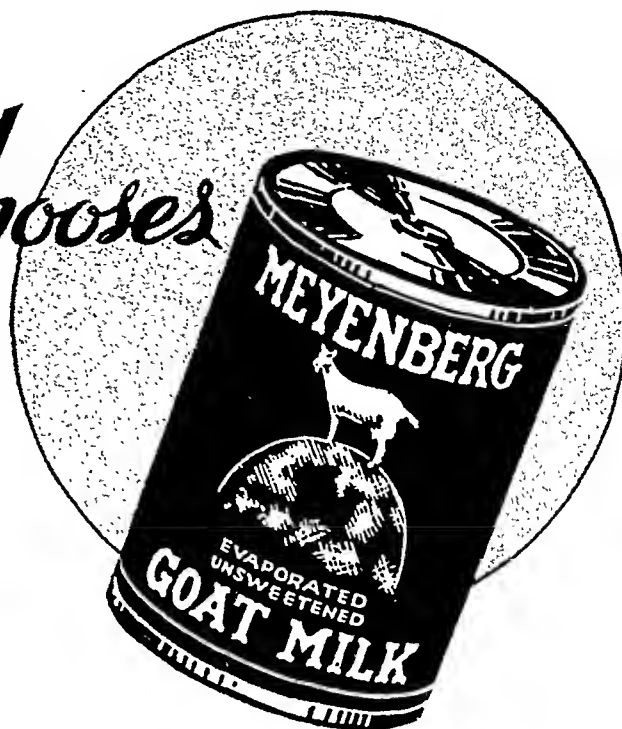
WEEKLY \$42 to \$56  
Single—\$84 to \$112  
Double, including meals  
and private bath

## HOTEL CHARLOTTE HARBOR

PUNTA GORDA, WEST COAST OF FLORIDA

# *The Doctor Chooses*

And every month more and more physicians are choosing Meyenberg Evaporated Goat Milk for their Food Allergy, Tuberculosis and difficult pediatric cases.



## **BECAUSE**

Goat milk protein is non-allergic and forms a fine, easily digested curd, and

## **BECAUSE**

The fat in goat milk is in fine globules of easily saponified oleates, and

## **BECAUSE**

The minerals of goat milk are in splendid proportion and quantitatively high, and

## **BECAUSE**

Meyenberg Evaporated Goat Milk is easily available, economical and bacteria-free.

If, so far, you have not chosen Meyenberg Evaporated Goat Milk, Doctor, send for the generous clinical size and descriptive literature.

---

## **GOAT MILK PRODUCTS CO.**

1039 South Olive Street

Los Angeles, California

---

Your druggist can now be supplied through any McKesson & Robbins wholesale house.

a subtotal removal of the lesser curvature of the stomach, spur formation by partial closure of the end of the stomach and vertical position of the stoma in the standing position of the patient. The jejunum is anastomosed to the stomach near its origin, forming a short loop. The Author believes that the long loop gastro-jejunal anastomoses predispose to gastro-jejunal ulcers. A well defined spur is formed at the lesser curvature border of the cut end of the stomach and the attachment of the jejunum is placed so as to reinforce this spur. At the junction of the greater curvature of the stomach with the jejunum, a spur is definitely avoided. These steps prevent retrograde filling of the duodenum with stomach contents.

N. W. Swinton, Boston.

RAND, C. W.

*Tuberculous Abscesses of the Brain Secondary to Tuberculosis of the Cecum. S. G. and O., Vol. 60, No. 2, pp. 229-235, Feb. 1, 1935.*

Not infrequently the central nervous system is invaded by tuberculosis which usually manifests itself there in the military form, or, less frequently, as single or multiple tuberculomata. The pathology of tuberculous abscess of the brain differs from that of tuberculous abscesses elsewhere in that it does not involve the various stages of granu-

lomatous changes to be expected from an organism of this nature. There is probably a primary period of localized encephalitis, a secondary period of softening, and a final period of capsule formation in the development of a true abscess.

In a review of the literature many cases of tuberculous involvement of the brain secondary to involvement of the cranial bones, or meninges, were found.

The Author reports in minute detail one case of true tuberculous abscesses of the brain associated with tuberculosis of the cecum.

Six figures and a bibliography accompany the article.

N. M. Percy, Chicago.

## ERROR

In the December Journal on page 598, an unfortunate omission was made in not stating the Journal in which Prof. William Boyd's article on Polycythemia appeared. The correct reference was as follows: American Journal of the Medical Sciences, v. 187, pp. 589-594, May, 1934.

# Viable Bacteria Reduced To Zero (Or Near Zero)

In 15 series of samples of the defecate from a number of human subjects. The subjects were not injured by the medication, as determined by thorough clinical and laboratory examinations immediately after cessation of medication and for a number of months subsequent thereto.

The medications employed were two saponaceous glycerites of Alpha Naphthol designated:

## ALPHA NAPH CO AND JELLY OF ALPHA NAPH CO

The Alpha Naph Co was taken in water and orange juice. The "Jelly" was administered in enteric coated capsules opening in the intestinal tract.

A resume of the reports, and adequate supplies for clinical test, will be gladly sent to any physician interested, with our compliments.

**CAREL LABORATORIES**  
REDONDO BEACH - - - CALIFORNIA

## Functional May Lead to Organic

Symptoms may point to trouble in the gastrointestinal tract.



## TAUROCOL Bile Salts Tablets

have proven very valuable in allaying the functional troubles in the gastrointestinal tract, permitting of the proper diagnosis.

In cases where the diagnosis is apparent and where troubles in the gastrointestinal tract are only sympathetic, the application of bile salts therapy through the administration of TAUROCOL has been found very valuable in allaying the symptoms while the organic trouble was properly treated.

*Clinical Record Forms for the asking.  
Samples and information on request.*

**The Paul Plessner Co.**

Detroit - - - Michigan

J. D. 1-36

## SECTION I—*Clinical Medicine: Diseases of Digestion*

### The Incidence and Biological Characteristics of the Hemolytic *Bacillus Coli* in the Intestinal Tract of Patients with Chronic Ulcerative Colitis\*

By

EDITH E. NICHOLLS, M.D.†  
NEW YORK, NEW YORK

IN 1934 an investigation was carried out by the Author relating to the incidence and biological characteristics of the hemolytic *Bacillus coli* in the stools of healthy individuals. Results of this study showed that the hemolytic *Bacillus coli* was a normal inhabitant of the intestinal tract and that if several stool specimens from the same person were examined, it was invariably found in at least one of them.

The presence of this organism in healthy individuals, however, has no bearing on the role that this same organism may play in pathological conditions of the intestinal tract. Throughout the literature there are equivocal statements concerning the significance of the hemolytic *Bacillus coli* in ulcerative colitis and other intestinal disorders. Many investigators have treated patients with vaccine, Dorst and Morris 1930 (1), Mateer and Baltz 1932 (2), Niles and Torrey 1934 (3), and serums. Vincent 1930 (4), Schwartzman and Winkelstein 1934 (5), made from this organism, but no convincing experimental data has been produced to demonstrate that the hemolytic *Bacillus coli* is of etiological importance in diseases of the gastrointestinal tract.

Schmidt, in 1909 (6), Dudgeon, Wordley and Bawtree 1921 (7), and Mateer and Baltz 1932 (2) studied the incidence of the hemolytic *Bacillus coli* in the stools of patients with "diarrhea" and colitis and found that it is approximately the same as in those of normal people. On the other hand, Meyer and Lowenberg 1924 (8), Dudgeon 1926 (9), and Niles and Torrey 1934 (3) found the percentage markedly higher in the group of patients with disorders of the gastrointestinal tract.

#### THE PRESENT STUDY

The present report is based on a study of the *Bacillus coli* recovered from fecal material removed from ulcers in the colons of patients suffering from chronic ulcerative colitis. The specimens were obtained from patients in the gastrointestinal clinic of the New York Hospital, through the courtesy of Dr. Thomas T. Mackie. In all of these cases there was a definite diagnosis of chronic ulcerative colitis based on the history and clinical findings. Forty-two patients were studied.

\*From the New York Hospital, and the Department of Medicine, Cornell University Medical College, New York City.  
†With the technical assistance of Herman P. Saltz, B.S.  
Submitted August 30, 1935.

24 males and 18 females. The youngest patient was 13 years of age, the oldest, 57, and the average age was 34.7 years. The duration of the ulcerative colitis varied from 3 months to 18 years, with an average of 3.9 years. In a high percentage of cases, several proctoscopic smears from the same patient were examined. Altogether, 135 specimens were analyzed.

#### TECHNIC

The culture was obtained by passing a long, sterile swab through the proctoscope and rubbing it over the surface of one of the ulcers. The swab was then placed in a tall, sterile test tube and was sent to the laboratory. As soon as it was received it was passed over the surface of an Endo's plate and the plate was incubated for twenty-four hours. In approximately 10 per cent of the samples there was such a small amount of material on the swab that very little or no growth was obtained on the Endo's plate. Therefore, in order to avoid losing a culture, one c.c. of sterile broth was put into the test tube containing the swab, after the Endo's plate had been streaked, and the tube was allowed to remain in the room overnight. If no growth, or only a few colonies, appeared on the Endo's medium, another plate was streaked and in this way a good growth was always obtained.

One hundred colonies were then transferred to a blood agar plate and the percentage of hemolytic *Bacillus coli* was obtained by the method described in a previous publication by the Author in 1934 (10).

#### RESULTS OF PROCTOSCOPIC SMEARS

One hundred and thirty-five proctoscopic smears from 42 patients with chronic ulcerative colitis were cultured and the hemolytic form of the *Bacillus coli* was found in 84, or 62.2 per cent of the samples (Table I). In 45, or 53.6 per cent of the 84 cultures the hemolytic *Bacillus coli* was present in large numbers (50 to 100 per cent). If we consider only the first swab specimen from each patient, hemolytic *Bacillus coli* organisms were present in 26, or 61.9 per cent of the 42 cases.

From 28 of the patients, repeated swab cultures were obtained, the number varying from 2 to 10 from a single patient. Specimens were taken at intervals ranging from one week to several months, and 13 patients were studied over a period of one to two years. In 22, or 78.6 per cent of the 28 patients, hemolytic

*Bacillus coli* was present in at least one of the specimens studied. In the 6 negative cases, 4 patients had 2 cultures only and 2 had 4 cultures.

In Table II are recorded the results of the examination of specimens from 15 patients from whom 4 or

TABLE I

*Relation of Positive Results of the Hemolytic Bacillus coli to the Number of Proctoscopic Smears Examined*

|                                  | Number of individuals | Positive for hemolytic B. coli |          | Negative for hemolytic B. coli |          |
|----------------------------------|-----------------------|--------------------------------|----------|--------------------------------|----------|
|                                  |                       | Number                         | Per cent | Number                         | Per cent |
| First or one specimen submitted  | 42                    | 26                             | 61.9     | 16                             | 38.1     |
| Two or more specimens submitted  | 28                    | 22                             | 78.6     | 6                              | 21.4     |
| Four or more specimens submitted | 15                    | 15                             | 100.0    | 0                              | 0        |

Total number of specimens submitted was 125, of which 84, or 67.2 per cent, were positive for hemolytic *Bacillus coli*.

more proctoscopic smears had been made. In 6 of the cases, all of the cultures studied contained hemolytic *Bacillus coli*, while in the other 9 cases, from 14.3 to 80 per cent of the smears showed the nonhemolytic type. In the case of no individual was the hemolytic organism absent from every culture examined, although there was a wide variation in the quantity of the hemolytic type present in the consecutive samples. As a representative example, the consecutive specimens from the patient B.G. ran as follows: 89, 100, 0, 23, 40, 0, and 48 per cent positive for the hemolytic *Bacillus coli*.

The hemolytic *Bacillus coli* colonies showed a variation in the size of the hemolytic zone on blood agar similar to that originally described by Schmidt (6). Seventy-two per cent of the strains fell into his "group one," 19 per cent into "group two," and 2 per cent into "group three." However, an organism was recovered from 7 per cent of the 96 hemolytic strains that had a much larger zone of hemolysis than the "group one" of Schmidt. In 11 cases two types of hemolytic colonies appeared in the same culture.

TABLE II

*Results of Repeated Examination of Proctoscopic Smears From the Same Individual*

| Patients | Total specimens | Positive for hemolytic <i>Bacillus coli</i> |          | Negative for hemolytic <i>Bacillus coli</i> |          |
|----------|-----------------|---------------------------------------------|----------|---------------------------------------------|----------|
|          |                 | Number                                      | Per cent | Number                                      | Per cent |
| R. G.    | 10              | 2                                           | 20       | 8                                           | 80       |
| G. P.    | 9               | 5                                           | 55.5     | 4                                           | 44.5     |
| R. K.    | 8               | 8                                           | 100      | 0                                           | 0        |
| L. D.    | 7               | 6                                           | 85.7     | 1                                           | 14.3     |
| B. G.    | 6               | 4                                           | 66.7     | 2                                           | 33.3     |
| S. E.    | 6               | 6                                           | 100      | 0                                           | 0        |
| G. C.    | 6               | 6                                           | 100      | 0                                           | 0        |
| J. L.    | 5               | 1                                           | 20       | 4                                           | 80       |
| J. H.    | 5               | 3                                           | 60       | 2                                           | 40       |
| S. F.    | 5               | 2                                           | 40       | 3                                           | 60       |
| P. S.    | 4               | 4                                           | 100      | 0                                           | 0        |
| M. B.    | 4               | 4                                           | 100      | 0                                           | 0        |
| M. J.    | 4               | 3                                           | 75       | 1                                           | 25       |
| L. T.    | 4               | 2                                           | 50       | 2                                           | 50       |
| D. D.    | 4               | 4                                           | 100      | 0                                           | 0        |

## CULTURAL AND BIOLOGICAL CHARACTERISTICS OF THE *BACILLUS COLI* STRAINS

Various tests were carried out on the strains of the hemolytic and nonhemolytic *Bacillus coli* for their identification. These tests were performed as soon as

possible after isolation of the strains. All of the organisms grew well in litmus milk, with the production of acid and clot. On Russell's medium they gave the characteristic appearance with acid and gas in the butt and acid in the slant. None of the strains liquefied gelatin at 22 degrees Centigrade.

The Voges-Proskauer and methyl-red tests were carried out on the strains according to the method described by Clark and Lubs (11), and the technique followed was that outlined by Levine (12). All of the strains were Voges-Proskauer negative and methyl-

TABLE III

*Comparison of the Hemolyzing Property of the Hemolytic *Bacillus coli* on Human Red Blood Cells\**

| Strain | First series         |                    | Second series        |                    |
|--------|----------------------|--------------------|----------------------|--------------------|
|        | 24 hours<br>0.85 0.5 | 1 hour<br>0.85 0.5 | 24 hours<br>0.85 0.5 | 1 hour<br>0.85 0.5 |
| 16     | C C                  | C C                | C C                  | C C                |
| 34     | C C                  | C C                | C C                  | C C                |
| 18     | C C                  | C C                | C C                  | C C                |
| 165    | C C                  | C C                | C C                  | C C                |
| 180    | C C                  | C C                | C C                  | C C                |
| 184    | C C                  | C C                | C C                  | C C                |
| 68     | C C                  | I 1                | C C                  | C C                |
| 177    | C C                  | I 1                | C I                  | C C                |
| 31     | C C                  | C C                | C C                  | M M                |
| 131    | C C                  | M M                | C C                  | M M                |
| 79     | C C                  | M M                | C C                  | M M                |
| 9      | C C                  | M M                | C C                  | M M                |
| 11     | C C                  | M M                | C C                  | M M                |
| 108    | C I                  | M M                | C I                  | M M                |
| 183    | C C                  | T T                | C C                  | M M                |
| 138    | C C                  | T T                | C C                  | T T                |
| 167    | C C                  | T T                | C C                  | T T                |
| 88     | C C                  | T T                | C C                  | T T                |
| 145    | C C                  | T T                | C C                  | T T                |
| 122    | C C                  | T T                | C C                  | M T                |
| 184    | C C                  | T T                | I C                  | T T                |
| 23     | C C                  | T T                | C C                  | T T                |
| 101    | I C                  | T T                | I I                  | T T                |
| 75     | C C                  | T T                | M M                  | T T                |
| 170    | M M                  | M M                | I M                  | M M                |
| 162    | M T                  | M T                | M T                  | M T                |
| 21     | M M                  | T T                | M M                  | T T                |
| 181    | M M                  | T T                | M M                  | T T                |
| 178    | M M                  | T T                | T M                  | T T                |
| 182    | M T                  | T T                | T T                  | T T                |
| 179    | T T                  | T T                | T T                  | T T                |
| 86     | T T                  | T T                | T T                  | T T                |
| 135    | T T                  | T T                | T T                  | T T                |

\*C: hemolysis of all the red cells. 1: hemolysis of nearly all of the red cells. M: distinct coloration of the whole medium. T: slight tingeing of the medium above the red cells. 24 hours: packed red blood cells added at time of inoculation and incubated 24 hours. 1 hour: packed red blood cells added after 24 hours of incubation and incubated an additional hour. 0.85 and 0.5: strengths of sodium chloride in peptone water medium.

red positive, which results conform to the usual reaction for *Bacillus coli*.

**Sugar fermentations.** Tests were carried out to determine the action of the *Bacillus coli* strains recovered from swab cultures on the various sugars. The mediums were prepared and the tests were carried out as described in the previous article (10). The sugars studied in that investigation were again employed and, in addition, salicin, dulcitol, and indol.

All of the strains examined fermented lactose, maltose, glucose, and mannite with the production of acid and gas. All of the strains produced indol in peptone solution. Twenty-seven of the 93 nonhemolytic organisms and 25 of the 68 hemolytic strains formed acid and gas in saccharose. Of the hemolytic strains, 44 fermented salicin, and 36, dulcitol. Of the nonhemolytic organisms, 54 acted upon salicin and 51, dulcitol. A



more detailed classification of the organisms according to their sugar reactions will be found in a subsequent article.

*Hemolysis tests.* The method described by Dudgeon, Wordley and Bawtree (7) was the one employed

TABLE IV

*Comparative Virulence for White Mice of 64 Hemolytic and 71 Nonhemolytic Strains of Bacillus coli*

| Minimum lethal doses c.c. | Hemolytic Bacillus coli Number | Bacillus coli Per Cent | Nonhemolytic Bacillus coli Number | Bacillus coli Per Cent |
|---------------------------|--------------------------------|------------------------|-----------------------------------|------------------------|
| 0.5                       | 1                              | 1.6                    | 5*                                | 7.0                    |
| 0.3                       | 4                              | 6.2                    | 15                                | 21.1                   |
| 0.1                       | 14                             | 21.8                   | 25                                | 35.2                   |
| 0.05                      | 24                             | 37.5                   | 19                                | 26.8                   |
| 0.01                      | 12                             | 18.8                   | 3                                 | 4.3                    |
| 0.005                     | 9                              | 14.1                   | 4                                 | 5.6                    |

\*The M.L.D. for one nonhemolytic strain was 0.8 c.c. and is included in this group.

in the examination of the various strains of the *Bacillus coli* for their capacity to produce hemolysis of red blood cells. Human blood was used and the test was performed twice, with a week's interval between each analysis.

Altogether, 32 strains of the *Bacillus coli* showing hemolysis of the red cells on rabbit blood agar were tested. A representative number of strains from each of the three groups was selected and the results of the study are shown in Table III. The organisms possessing active hemolyzing properties showed very little difference in the degree of hemolysis present in the 0.85 per cent and the 0.5 per cent sodium chloride mediums. In the tubes to which human red blood cells had been added before incubation, the degree of hemolysis was more marked than in those to which cells were added the following day.

All of the strains belonging to "group one," that is, those showing a large zone of hemolysis on rabbit blood agar, manifested complete hemolysis of the red cells when incubated with the blood for twenty-four hours. When they were incubated for one hour, there was a wide variation from complete hemolysis to only a trace. The "group two" strains showed only a moderate amount of hemolysis and the "group three" strains showed only a trace of hemolysis.

*Virulence tests.* It was a matter of interest to determine the comparative virulence of the hemolytic and the nonhemolytic strains of the *Bacillus coli*. White mice of approximately twenty to twenty-five grams were used for the test, and the method employed was similar to the one previously outlined (10).

The test for virulence was carried out on 64 hemolytic and 71 nonhemolytic strains of the *Bacillus coli*. In Table IV is shown, under the various dilutions of the cultures, the minimal lethal dose for the different strains. It may be seen that 70.4 per cent of the hemolytic strains and 36.7 per cent of the nonhemolytic were virulent for white mice in doses of 0.05 or less. Thus, the hemolytic organisms were somewhat more virulent for white mice than the nonhemolytic.

*Agglutination reactions.* In order to determine whether there was any biological relationship between the hemolytic and the nonhemolytic strains of the *Bacillus coli* recovered from proctoscopic smears and those recovered from the stools of healthy individuals, agglutination tests were carried out with the serums

from four rabbits immunized against two hemolytic and two nonhemolytic strains of *Bacillus coli*, previously recovered from stool cultures of normal people. The four immune serums were tested for agglutinins against 40 strains of the *Bacillus coli*, 19 of which were hemolytic and 21 nonhemolytic.

The agglutination tests were carried out according to the method previously described (10). The *Bacillus coli* strains were divided into two main groups, the hemolytic and the nonhemolytic. These, in turn, were separated into two subgroups, the communior and communis, depending upon their reaction to saccharose.

Agglutination tests were carried out with the four immune serums, NH-8 cs.; NH-21 cr.; H-46 cs.; and H-62 cr. against 16 nonhemolytic communis strains, 5 nonhemolytic communior, 13 hemolytic communis, and 6 hemolytic communior.

From Table V it may be seen that the strains showed no tendency to fall into biological groups. Thus, of

TABLE V

*Titer of Agglutination Reactions With Four Serums From Rabbits Immunized Against Strains of Bacillus coli, One From Each of the Four Groups*

| Strain*   | Nonhemolytic immune serums |           | Hemolytic immune serums |          |
|-----------|----------------------------|-----------|-------------------------|----------|
|           | NH-8 cs.                   | NH-21 cr. | H-46 cs.                | H-62 cr. |
| NH-20 cs. | 1:5120                     | 1:80      | 1:160                   | 1:640    |
| NH-22 cs. | 1:5120                     | 1:160     | 1:1280                  | 1:5120   |
| NH-34 cs. | 1:5120                     | 1:40      | 1:80                    | 1:5120   |
| NH-16 cs. | 1:320                      | 1:2560    | 1:40                    | 1:80     |
| NH-29 cs. | 1:5120                     | 0         | 1:40                    | 1:2560   |
| NH-52 cs. | 1:5120                     | 0         | 1:320                   | 1:5120   |
| NH-31 cs. | 1:40                       | 0         | 1:80                    | 1:320    |
| NH-49 cs. | 1:80                       | 0         | 1:320                   | 1:5120   |
| NH-44 cs. | 1:5120                     | 0         | 1:320                   | 0        |
| NH-40 cs. | 1:320                      | 1:80      | 0                       | 0        |
| NH-57 cs. | 1:320                      | 0         | 1:80                    | 0        |
| NH-56 cs. | 0                          | 0         | 0                       | 0        |
| NH-46 cs. | 0                          | 0         | 0                       | 0        |
| NH-10 cs. | 0                          | 0         | 0                       | 0        |
| NH-9 cs.  | 0                          | 0         | 0                       | 0        |
| NH-30 cs. | 0                          | 0         | 0                       | 0        |
| NH-25 cr. | 1:5120                     | 0         | 1:640                   | 1:1280   |
| NH-38 cr. | 1:160                      | 1:1280    | 0                       | 0        |
| NH-61 cr. | 1:160                      | 0         | 0                       | 1:80     |
| NH-50 cr. | 0                          | 1:640     | 1:80                    | 0        |
| NH-27 cr. | 0                          | 0         | 0                       | 0        |
| H-18 cs.  | 1:640                      | 1:5120    | 1:40                    | 1:320    |
| H-13 cs.  | 1:40                       | 1:80      | 1:40                    | 1:80     |
| H-41 cs.  | 1:5120                     | 0         | 1:160                   | 1:640    |
| H-48 cs.  | 1:5120                     | 1:2560    | 1:80                    | 0        |
| H-23 cs.  | 1:320                      | 1:2560    | 0                       | 1:160    |
| H-39 cs.  | 1:160                      | 0         | 0                       | 1:320    |
| H-51 cs.  | 0                          | 0         | 0                       | 0        |
| H-43 cs.  | 0                          | 0         | 0                       | 0        |
| H-55 cs.  | 0                          | 0         | 0                       | 0        |
| H-47 cs.  | 0                          | 0         | 0                       | 0        |
| H-15 cs.  | 0                          | 0         | 0                       | 0        |
| H-17 cs.  | 0                          | 0         | 0                       | 0        |
| H-21 cs.  | 0                          | 0         | 0                       | 0        |
| H-37 cr.  | 1:320                      | 1:80      | 1:2560                  | 1:5120   |
| H-11 cr.  | 1:320                      | 1:80      | 1:160                   | 1:320    |
| H-62 cr.  | 1:640                      | 1:640     | 1:320                   | 1:320    |
| H-54 cr.  | 1:80                       | 0         | 1:160                   | 1:80     |
| H-42 cr.  | 0                          | 0         | 0                       | 0        |
| H-45 cr.  | 0                          | 0         | 0                       | 0        |

\*NH indicates nonhemolytic; H, hemolytic; cs., communis; cr., communior.

the 16 strains in the nonhemolytic communis group, about 50 per cent were agglutinated by NH-8 cs. of the same group. Most of these same strains were agglutinated, as well, by serums NH-21 cr., H-46 cs., and H-62 cr. of the other three groups. Three strains

were agglutinated by two serums only, and five strains failed to be agglutinated by any of the serums.

The strains in the other three groups showed a marked tendency for agglutination similar to that described above for the nonhemolytic communis organisms. There seemed to be no type specificity. With a few exceptions, the strains were either agglutinated by all four serums, or failed to be agglutinated by any of them.

#### A COMPARISON OF THE INCIDENCE AND BIOLOGICAL CHARACTERISTICS OF THE HEMOLYTIC *BACILLUS COLI* RECOVERED FROM THE INTESTINAL TRACTS OF HEALTHY INDIVIDUALS AND OF PATIENTS WITH CHRONIC ULCERATIVE COLITIS

One hundred and thirty-five proctoscopic smears from 42 patients with chronic ulcerative colitis were cultured for the presence of the hemolytic *Bacillus coli* and this organism was found to be present in 84, or 62.2 per cent, of the specimens. The results obtained from the study of single and repeated specimens from the same patient were of particular interest. In the 42 first or single samples cultured the incidence of the hemolytic *Bacillus coli* was 61.9 per cent. In the 28 cases where two or more specimens from the same person were studied the figure rose to 78.6 per cent, and in the 15 instances where 4 or more cultures were examined hemolytic *Bacillus coli* was recovered from 100 per cent of the patients.

In 1934 an investigation was carried out by the Author concerning the incidence and biological characteristics of the hemolytic *Bacillus coli* in the stools of healthy individuals (10). In the study, one hundred and sixty-nine specimens of stools from 73 persons were cultured and the hemolytic *Bacillus coli* was found to be present in 114, or 67.4 per cent of the samples. In the 73 first or single specimens studied the incidence was 36.2 per cent. In the 25 cases where two or more specimens from the same individual were studied the figure was 88 per cent, and in 12 instances where 4 or more cultures were examined hemolytic *Bacillus coli* was found in 100 per cent of the subjects.

If one compares the frequency of occurrence of the hemolytic type of the *Bacillus coli* recovered from patients with chronic ulcerative colitis and from healthy individuals, the results are found to be surprisingly similar in each group. In each study the percentage of patients showing the presence of the hemolytic *Bacillus coli* increased with the number of specimens per patient examined, and where four or more samples were studied the hemolytic type was found to be present in every subject. From these figures it seems reasonable to conclude that the hemolytic *Bacillus coli* is a normal inhabitant of the intestinal tract of patients with chronic ulcerative colitis as well as of healthy people and that the incidence is no higher in the colitis patients than in the normal subjects.

All of the hemolytic and nonhemolytic strains of the *Bacillus coli* recovered from the colitis patients conformed to the same cultural reactions as those from the healthy individuals. There were no unusual forms of the *Bacillus coli* recovered from the colitis cases as compared with the strains recovered from normal stools.

The majority of the hemolytic strains tested showed active hemolyzing properties for the red cells of human blood when incubated for twenty-four hours. Seven strains which showed only a small zone of hemolysis on rabbit blood agar had only moderate or slight hemolyzing properties for human red blood cells. These results were practically identical with those obtained from the study pertaining to the healthy individuals.

The virulence of the strains of the *Bacillus coli* recovered was an interesting feature in the study, and especially as seen in the hemolytic type. In the study of the stools for normal people the hemolytic organisms were found to be somewhat more virulent for white mice than the nonhemolytic, but the difference was not sufficiently striking to be significant. In the present investigation, the hemolytic strains were definitely more virulent than the nonhemolytic. If, however, one compares the hemolytic and nonhemolytic strains of the two studies, this difference is found to be due to a decrease in the virulence of the nonhemolytic strains rather than to an increase in that of the hemolytic. Of the hemolytic strains, 70.4 per cent of those recovered from colitis patients were able to kill the mouse in doses of 0.05 c.c., or less, while as many as 65 per cent of those from healthy individuals showed the same virulence. Of the nonhemolytic strains from the colitis patients, 36.7 per cent of the strains and of those from normal intestinal tracts 50 per cent required 0.05 c.c., or less, of the culture to kill the mouse.

It was considered of some importance to determine whether any immunological relationship existed between the strains of *Bacillus coli* obtained from patients with chronic ulcerative colitis and those from healthy individuals. A representative number of strains from each of the four groups, namely, the hemolytic communior, hemolytic communis, nonhemolytic communior and nonhemolytic communis, was selected and agglutination tests were carried out with 4 immune rabbit serums, one from each group, which had previously been used for agglutination tests with the strains from normal stools. A high percentage of the strains of each group were agglutinated, at least in some degree, by the immune serum of their own group and also by those of the other three groups. Thus, as was found in the previous study, a biological analogy seemed to exist, not only within the membership of each group, but also between the strains of all four groups, regardless of type. In addition, a definite relationship was found to exist between the strains of *Bacillus coli* obtained from proctoscopic smears from patients with chronic ulcerative colitis and the strains obtained from stool specimens from healthy individuals.

#### CONCLUSIONS

1. The hemolytic type of the *Bacillus coli* may be recovered from the intestinal tract of patients with chronic ulcerative colitis in a high percentage of cases. If four or more specimens from a single individual are examined, it is shown to be present in one hundred per cent of the cases. The results are similar to those obtained from a study of stool cultures from healthy individuals.

2. The hemolytic strains of the *Bacillus coli* recovered from proctoscopic smears were found to be

somewhat more virulent for white mice than the non-hemolytic. However, the virulence of the hemolytic type was approximately the same as for those recovered from the stools of healthy persons, while the non-hemolytic showed a somewhat lower virulence.

3. The *Bacillus coli* recovered from the intestinal tract of patients with colitis appear to be heterologous strains having agglutinins more or less in common

with each other and with those isolated from the stools of healthy people.

4. From this study it may be concluded that in incidence and biological characteristics, hemolytic and nonhemolytic strains of *Bacillus coli* recovered from proctoscopic smears of patients with chronic ulcerative colitis, differ in no respect from those obtained from stool specimens of healthy individuals.

#### REFERENCES

1. Dorst, S. E., and Morris, R. S.: Bacterial hypersensitivity of the intestinal tract. *Am. J. M. Sc.*, 180, 650, 1930.
2. Mnteer, J. G., and Baltz, J. I.: An evaluation of stool vaccines in chronic irritable colon therapy. *Ann. Int. Med.*, 5, 952, 1932.
3. Niles, W. L., and Torrey, J. C.: The clinical significance of *B. coli* hemolyticus. *Am. J. M. Sc.*, 187, 30, 1934.
4. Vincent, M. H.: Rôle de la toxi-infection colibacillaire dans certaines entéropathies chroniques. Action de la sérothérapie anticolibacillaire dans ces états morbides. *Bull. Acad. Méd., Paris*, 103, 431, 1930.
5. Schwartzman, G., and Winkelstein, A.: A new type of serum therapy for the treatment of non-specific ulcerative colitis. *Am. J. Digest. Dis. and Nutrit.*, 1, 582, 1934.
6. Schmidt, T.: Untersuchungen über Hämolyse bei *Coli*- und anderen Darmbakterien. *Zentralbl. f. Bakt.*, (Abt. 1), Orig., 50, 359, 1909.
7. Dudgeon, L. S., Wordley, E., and Bawtree, F.: On *Bacillus coli* infections of the urinary tract, especially in relation to hemolytic organisms. *J. Hyg.*, 20, 137, 1921.
8. Meyer, K., and Löwenberg, W.: Zur Frage der serologischen Einheitlichkeit der Colibacillen. *Klin. Wchnschr.*, 3, 836, 1924.
9. Dudgeon, L. S.: A study of the intestinal flora under normal and abnormal conditions. *J. Hyg.*, 25, 119, 1926.
10. Nicholls, E. E.: The incidence and biological characteristics of the hemolytic *Bacillus coli* in the stools of healthy individuals. *J. Clin. Invest.*, 13, 479, 1934.
11. Clark, W. M., and Lubs, H. A.: The differentiation of bacteria of the colon-aerogenes family by the use of indicators. *J. Infect. Dis.*, 17, 160, 1915.
12. Levine, M.: The correlation of the Voges-Proskauer and methyl-red reactions in the colon-aerogenes group of bacteria. *J. Infect. Dis.*, 18, 355, 1916.

## The Takata-Ara Test of Liver Function

By

THOMAS B. MAGATH, M.D.\*  
ROCHESTER, MINNESOTA

**T**AKATA and Ara. in 1925, proposed a test based on a colloidal phenomenon manifested by the spinal fluid to differentiate between meningitis and syphilitic involvement of the central nervous system. This test has enjoyed apparently wide usage in Europe as a substitute for other colloidal tests on spinal fluid, but the reports do not support the contention that it has advantages over the gold or benzoin colloidal methods. The same year Takata extended the test to the blood serum of patients with pneumonia. By the test he proposed to differentiate lobar and lobular pneumonia but no further work has been reported.

These Japanese investigators thought the reaction was due to change in the relative amounts of albumin and globulin in the serum. Since the test involves the flocculation of a mercury oxy sol, and since this seemed to take place when relative excesses of globulin were present, so that the colloid was no longer protected, it was assumed that this phenomenon depended on a reversal or partial reversal of the ratio of albumin to globulin.

Jezler realized that such a protein shift was not peculiar to the blood of patients with pneumonia but often occurred in parenchymatous diseases of the liver. So he applied the test in a variety of such cases and pointed out that a major number of serums from patients with cirrhosis gave a positive test—in his series, in thirty-eight out of forty-two cases. He noted positive tests in other cases of hepatic disease and in some cases of nephritis, but in the twelve cases of parenchymatous jaundice studied by him and in seventeen cases of tumors of the liver he obtained only negative tests. He pointed out that the test could be

performed on ascitic fluid as well as on serum, and this has been verified.

Since the publication of the work of Jezler, others have studied the test with reference to its value in detecting disease of the liver. The impression is gained from the numerous papers published in Europe, and from the few now recorded in the American literature, that the test is thought to be fairly specific for cirrhosis, but that early in the disease the test is negative, and further, that the correlation between positive Takata-Ara tests and reversals of the albumin-globulin ratio is high.

Nevertheless, a careful reading and study of protocols leaves one in doubt as to the specificity of the test in cirrhosis. Thus Heath found the test to be positive in 60 per cent of cases of cirrhosis, although it was positive in nearly all advanced cases. He found that the reaction was positive in nine of thirty-one cases of hepatic injury and disease and in only 3 per cent of general medical cases in which damage to the liver was not diagnosed. Shindel and Barth found the test positive in 83.8 per cent of cases of cirrhosis but noted that massive involvement of the liver, especially with carcinoma, also gave positive tests. Rohrer believed the test was frequently positive in disease of the liver which was not cirrhosis and that negative tests did not exclude cirrhosis.

Van Ginkel noted that the test, while usually positive in cirrhosis, was also positive in advanced carcinoma and syphilis; on the other hand, however, Crane found it highly specific for cirrhosis and acute yellow atrophy, but negative for neoplasms, nephritis, and active pulmonary tuberculosis, although Pongor found 90 per cent of cases of this last gave positive tests.

\*Division on Clinical Pathology, Section on Parasitology, The Mayo Clinic.  
Submitted August 19, 1935.

Ragins obtained 114 positive results in 276 cases. Of these only 50 per cent were cases of cirrhosis, the other half being a variety of hepatic diseases, tumors, infections, renal disease, cardiac disease, and so forth. Ninety-eight per cent of his patients with cirrhosis gave a positive test, but he remarked that for latent

TABLE I  
*Takata-Ara Test of Liver Function*

|                                  | Takata-Ara test |          |
|----------------------------------|-----------------|----------|
|                                  | Positive        | Negative |
| Albumin-globulin ratio, reversed | 12              | 2        |
| Albumin-globulin ratio, normal   | 9               | 39       |
| Cells of liver involved          | 25              | 25       |
| Cells of liver not involved      | 4               | 29       |
| Bromsulphalein test, positive    | 25              | 29       |
| Bromsulphalein test, negative    | 4*              | 24       |
| Cirrhosis present                | 16              | 9        |
| Cirrhosis absent                 | 16              | 40       |
| Cancer, liver                    | 7               | 2        |
| van den Bergh reaction, direct   | 22              | 19       |
| van den Bergh reaction, indirect | 9†              | 34       |

\*Liver not involved.

†In four of these cases liver not involved.

hepatic damage the test is not entirely reliable. He was unable to correlate the protein content of the serum with the reaction.

#### METHOD

The method of performing the test has undergone some slight modification at the hands of various investigators, and at this Clinic it has been performed following the suggestions of Heath.

Into each of six small test tubes (100 by 13 mm.) is placed 1.0 c.c. of 0.9 per cent sodium chloride. To the first tube 1.0 c.c. of serum is added and the contents thoroughly mixed. One cubic centimeter is then removed and added to the second tube. After mixing, 1.0 c.c. is transferred from the second to the third tube, and so on until the sixth tube, from which 1.0 c.c. is discarded. The dilutions of serum thus range from 1:2 to 1:64. To each of the tubes 0.25 c.c. of 10 per cent sodium carbonate is added and the contents well shaken. Then 0.15 c.c. of mercuric chloride is added to each tube and the tubes are again shaken. The mixtures are allowed to stand at room temperature over night and readings are made at sixteen to twenty-four hours. The readings are divided into five groups: strongly positive, positive, weakly positive, suspicious, and negative. A strongly positive reaction is characterized by a maximal precipitate in any one tube or some precipitate in at least five tubes, the maximal precipitate on settling filling at least the lower third of the fluid column. A positive reaction occurs when there is a definite but not a maximal precipitate in any one tube or some precipitate in at least three tubes. A weakly positive reaction is present when there is a definite but minimal precipitate in any one or two tubes, and a suspicious reaction is present when there is a doubtful precipitate in any two tubes. The reaction is considered negative when there is no flocculent precipitate. A definite, pearly flocculent precipitate must be present to interpret a reaction as positive. Granular or flaky precipitates are disregarded.

The impression gained from performing the Takata-Ara test is that slight flocculations and precipitations occasionally occur and that these are difficult to interpret. The so-called "suspicious" positive reaction is especially difficult to read, and its significance is, therefore, extremely questionable. In the series here reported there were six reactions called suspiciously positive. In the tabulation these were considered negative; however, the liver was involved in four of the six cases, two being cases of carcinoma of the liver

and two of cirrhosis. From a technical standpoint it is impossible to identify the test accurately as positive unless a degree of precipitation is present sufficiently great to leave no doubt about the positiveness of the reaction.

#### RESULTS OF OBSERVATIONS

In order to test the value of the Takata-Ara reaction, a series of eighty-six consecutive cases in which the test was performed were studied (Table I). In each case a bromsulphalein test\* was also performed simultaneously. Qualitative and quantitative van den Bergh tests\*\* were done in eighty-three cases, and quantitative determinations of protein were made in sixty-two cases, all the tests being done on sixty-one patients. All these patients were carefully studied clinically, with special reference to the possibility of disease of the liver. The condition of the liver of twenty-seven patients was observed either at operation or at necropsy.

The diagnosis of cirrhosis was made on twenty-five patients, of whom sixteen gave a positive Takata-Ara test; however, sixteen other patients without cirrhosis also gave positive tests. Hepatic disease of some kind was diagnosed in fifty-three patients, the Takata-Ara test being positive in twenty-eight and negative in twenty-five instances. With four patients who apparently did not have involvement of the liver the Takata-Ara test was positive. Of nine patients with malignant conditions involving the liver, seven gave a positive Takata-Ara reaction. It was evident that the negative tests in cases of disease of the liver were for the most part obtained in cases of early lesions, or relatively small ones, and that, usually, obstructive lesions did not result in positive tests.

There was no evidence to suggest that changes in the total protein of the serum could be correlated with the Takata-Ara tests. In twelve cases in which there was a positive Takata-Ara test there was a reversal of the albumin-globulin ratio, while in nine there was a normal ratio; in two cases the ratio was reversed but the Takata-Ara test was negative. In only about half of the cases in which there was reversal of the albumin-globulin ratio was the liver involved, and in nine out of twenty-one cases of cirrhosis the ratios were reversed. Only one case, that of hypernephroma, had a reversed ratio and one in which involvement of the liver was not diagnosed. It should be noted that very few cases of disease of the kidney were included in the series. It is possible that the fibrinogen content of the serum has an influence on the Takata-Ara reaction and may account for Takata's results in cases of pneumonia.

The correlation between the Takata-Ara test and the bromsulphalein test was not high; only half the cases that showed dye retention gave a positive Takata-Ara test. There were four cases having a

\*The bromsulphalein test was performed by injecting, intravenously, 5 mg. of the dye per kilogram of body weight after the patient had abstained from food for twelve hours. Blood for a control was taken at the time of injection. One hour later a specimen was taken for testing. Serum was carefully obtained from the blood without mixing. To the specimen taken after an hour was added a drop of 10 per cent sodium hydroxide and the color was compared by transverse comparison with standards, using a part of the hour serum in front of the color tube. As a further control to the reading, the control serum was used after adding a drop of alkali to it. It requires experience and constant attention to details in order to have consistent results. A retention up to 6 per cent of the dye is considered negative; from 6 to 12 per cent, grade 1; from 12 to 24 per cent, grade 2; from 24 to 40 per cent, grade 3; and 40 per cent or more, grade 4. The standard equivalent to 40 per cent contains 4 mg. of bromsulphalein per 100 c.c.

\*\*Performed in Laboratory of Clinical Chemistry.

positive Takata-Ara test and a negative dye test in which the liver was not involved. Direct van den Bergh reactions were present when twenty-two Takata-Ara tests were positive and when twenty were negative. In nine cases with positive Takata-Ara tests, the van den Bergh reaction was indirect. In four of these cases the liver was not involved. Of the ten patients in the series diagnosed as having syphilis, five had a positive Takata-Ara test; the liver was evidently involved in these five cases.

The relation of the van den Bergh reaction to the presence or absence of injury to the liver is of great importance. In this series the reaction was direct in thirty-nine of fifty-two cases in which the liver was involved and in two in which the liver was not involved according to clinical diagnosis. These two cases were one of hypernephroma, in which there was also retention of dye and a reversal in the albumin-globulin ratio, and one of hemolytic jaundice, a type of case in which the liver is sometimes involved but in which it is difficult to detect such involvement clinically.

The results of the dye test in this series are quite significant. In fifty-one cases in which the liver was involved by disease the test was positive. The test was also positive in three cases in which the liver was thought to be uninvolved. These were cases of arthritis, hypernephroma, and facial neuralgia. In these three cases the dye retained was just sufficient to report the test as grade 1 (6 per cent of dye retained). In two cases there was evidence to justify the clinical diagnosis of involvement of the liver, but the report of the dye test was negative. In these two cases—retention of dye, although recorded as grade 0, was actually 4 per cent, and this is the upper limit of percentages which can be designated grade 0. These two cases were of tertiary syphilis, with clinical manifestations of hepatitis but with no positive laboratory tests, and of recurrent cholangitis, respectively, tests being done during a remission. The importance of dye retentions of grade 1 (up to 12 per cent retention) is brought out by the fact that of sixteen cases in which retention of grade 1 was present, involvement of the liver was surely present in thirteen and probably was present in one other.

#### COMMENT

From this series of cases and from a study of the results of others, it becomes clear that the Takata-Ara test on serum is a colloidal phenomenon which has as yet not been explained. It is, therefore, an empiric

TABLE II  
*Albumin-Globulin Ratio in Disease of Liver*

| Condition of liver          | Albumin-globulin ratio normal, cases | Albumin-globulin ratio reversed, cases |
|-----------------------------|--------------------------------------|----------------------------------------|
| Cirrhosis present           | 12                                   | 9                                      |
| Cirrhosis absent            | 36                                   | 4*                                     |
| Cells of liver involved     | 23                                   | 13                                     |
| Cells of liver not involved | 25                                   | 1†                                     |

\*Carcinoma of liver present in three of these cases, hypernephroma in the fourth.

†Hypernephroma.

test. It is evidently of no value in diagnosing types of pneumonia, and while it has been reported as useful in testing spinal fluids, it does not give positive reactions on serums in more than half of the cases of syphilis. The test is evidently not specific for either

injury to the liver or cirrhosis, but in the presence of hepatic disease a positive Takata-Ara test is more likely to indicate cirrhosis than other disease. About one-half of the patients with damage to the liver may be expected to yield a positive Takata-Ara test. If the

TABLE III  
*Comparison of Tests of Liver Function*

| Test                             | Cells of liver involved, cases | Cells of liver not involved, cases |
|----------------------------------|--------------------------------|------------------------------------|
| Takata-Ara test positive         | 23                             | 4*                                 |
| Takata-Ara test negative         | 25                             | 29                                 |
| Bromsulphalein test positive     | 51                             | 3†                                 |
| Bromsulphalein test negative     | 2†                             | 29                                 |
| van den Bergh reaction, direct   | 39                             | 2‡                                 |
| van den Bergh reaction, indirect | 13                             | 29                                 |

\*Cases of myocardial degeneration, adenoma of gall bladder, hemolytic icterus, and polycythemia, respectively.

†Cases of arthritis, hypernephroma, and facial neuralgia, respectively.

‡Hepatitis (?) and syphilis present in one case; recession in cholangitis in the other.

§Hypernephroma in one case, hemolytic icterus in the other.

injury is severe or of long standing, the incidence of positive reactions will increase. Early cirrhosis quite evidently does not produce changes which result in a positive Takata-Ara test. The degree of positiveness of the Takata-Ara test is not well correlated with the degree of liver disease, and it is evident that the subdivisions of the test are too fine for clinical use.

In 83 per cent of cases there is a correlation between the Takata-Ara test and a reversed albumin-globulin ratio, although some shifting from normal is observed in a higher percentage of cases (Table II). A reversed albumin-globulin ratio occurs about as frequently in cases of hepatic disease as does a positive Takata-Ara test.

If a direct van den Bergh reaction is used as a criterion of injury to the liver, it will be found to be reliable in about 80 per cent of cases. One may expect only about 1 per cent of cases to yield a direct test in the absence of clinical evidence of hepatic damage if careful ring tests are performed. Indirect van den Bergh reactions will occur until the damage to the liver is great enough to render the organ unable to excrete the changed bilirubin through the bile passages.

As compared with the bromsulphalein test, the Takata-Ara and van den Bergh tests and the albumin-globulin ratio are all far less sensitive in indicating hepatic injury (Table III). In this series almost every case (96 per cent) in which there was evident parenchymal hepatic injury or even moderate obstruction to the output of bilirubin, the dye test so indicated it. An important point is that in most instances dye retention of low grade indicated disease of the liver. A large share of the retentions of high grade occurred in cases of mechanical obstruction, and the test indicates in this series, as in others, that there is a failure of the liver to excrete the type of bilirubin commonly referred to as "direct reacting." Fundamentally, this is due to either physiologic or anatomic obstruction, and frequently the dye test indicates the obstruction long before the patient becomes jaundiced.

The desire of clinicians, however, is to have a test which will go farther than indicating a failure of the liver to excrete pigments properly, and it was hoped that the Takata-Ara test would aid in this regard. To a certain extent it does, in that mechanical obstruction



without much hepatic damage does not result in a positive Takata-Ara test. On the other hand, a considerable amount of parenchymatous hepatic damage must be present before the test becomes positive. That the test is not specific for cirrhosis is plainly evident, and if one can make use of the test at all in such diagnoses, it is just a matter of saying that, of the nonobstructive lesions of the liver, cirrhosis is among the most common, and hence that there is more chance that the lesion under such conditions is cirrhosis. Doubtless almost all advanced cases of cirrhosis will yield a positive Takata-Ara test. Evidently a moderate infiltration of cancer into the liver will cause changes which will result in a positive Takata-Ara test. There is no need of performing the test if the bromsulphalein test is negative, and perhaps rarely if the test is positive. Of patients with dye retention of grade 3 or 4, about half had positive Takata-Ara tests; the distribution of diagnoses did not seem to vary from those with negative Takata-Ara tests but it may indicate a more severe grade of hepatic damage when the Takata-Ara test is positive under such circumstances than when

the Takata-Ara test is negative. If this be true, then the Takata-Ara test is of more value in prognosis and in determining operative procedures than in diagnosis, for there is evidence that the test becomes less positive and even negative as the patient improves. It is questionable, however, whether it will prove more reliable than van den Bergh tests in this regard.

### SUMMARY AND CONCLUSIONS

The Takata-Ara test will be positive in slightly more than half of the cases in which there is parenchymatous hepatic damage when the injury has reached a moderately severe stage. The test is not specific for any one disease of the liver.

The test is correlated to a great extent with changes in the ratio of albumin to globulin, but the correlation is not an absolute one.

Although few false positive reactions are encountered, the test is not very sensitive.

The bromsulphalein test is highly specific in detecting that injury to the liver which results in its failure to excrete bilirubin properly.

### REFERENCES

1. Crane, M. P.: A modified mercuric chlorid reaction (Takata-Ara) in cirrhosis and in neoplasms of the liver. *Am. Jour. Med. Sc.*, 187:705-710, May, 1934.
2. van Ginkel, J. H. R.: Takata-Ara test in cirrhosis of liver. *Nederl. Tijdschr. v. Geneesk.*, 78:591-596, 1934.
3. Heath, C. W.: Takata-Ara test in the diagnosis of liver disease. *New England Jour. Med.*, 211:1077-1081, Dec. 13, 1934.
4. Jezler, Adolf: Die Takatase Kolloidreaktion in Serum und Körperflüssigkeiten und ihre Beziehungen zu Störungen des Eiweißstoffwechsels der Leber. *Ztschr. f. klin. Med.*, 114:739-756, 1930.
5. Pongor, F.: Über die Takata-Reaktion. *Beitr. z. Klin. d. Tuberk.*, 78:755-759, 1931.
6. Ragins, A. N.: The value of the Takata and Ara reactions as diagnostic and prognostic aid in cirrhosis of the liver. *Jour. Lab. and Clin. Med.*, 20:502-513, June, 1935.
7. Rohrer, Christian: Über Takata-Ara-Reaktion (Modifikation Jezler) bei Leberaffektionen. *Ztschr. f. klin. Med.*, 123:637-648, 1933.
8. Schindel, L., and Barth, E.: Die Bedeutung der Takata-Reaktion für die Diagnose der Lebererkrankungen in ihrem Verhältnis zur Galaktose- und Bilirubin-Belastung. *Klin. Wchnschr.*, 13:1355-1359, Sept. 22, 1934.
9. Takata, M.: Über eine Kolloidehemische Sero-Diagnostik der Lebererkrankung. *Tr. Sixth Congress For Eastern Assn. Trop. Med.*, 1:693-699, 1925.
10. Takata, M., and Ara, K.: Über eine neue Kolloidehemische Liquorreaktion und ihre Praktischen Ergebnisse. *Tr. Sixth Congress For Eastern Assn. Trop. Med.*, 1:667-671, 1925.

## The Hippuric Acid Test for Hepatic Function; Its Relation to Other Tests in General Use

By

ALBERT M. SNELL, M.D.†

and

JOHN E. PLUNKETT, M.D.‡

ROCHESTER, MINNESOTA

THE majority of tests now in clinical use for the study of hepatic function are designed to test the excretory function of the liver or its properties with regard to the metabolism of carbohydrate, protein, and fat. The latter group of tests has been somewhat disappointing in clinical use, because of the enormous reserve function of the liver in respect to its metabolic activities, and its regenerative ability. Difficulties also arise because in many cases extraneous factors, which may interfere with the results of the test, cannot be completely eliminated. The galactose tolerance test, because of its simplicity and the relatively satisfactory results which have been obtained by its use, is one exception, but there is little to indicate that one can de-

termine hepatic damage quantitatively by its use. The dye type of test of excretory function gives more valuable information in regard to the degree of hepatic damage than any one test in general use; however, such cannot be used satisfactorily in the presence of jaundice, and in fact, do not give a true picture of the degree of hepatic dysfunction in this condition. In cases of jaundice the most satisfactory idea of the extent of the hepatic lesion is often attained from a study of the level of bilirubinemia and variations in it. It is obvious that this factor may depend on the rate of destruction of blood and the degree of obstruction to the biliary passages, so that information obtained from this source may not be absolutely reliable. For these reasons, it is obviously desirable to devise tests of certain other functions of the liver, in the hope that

†Division of Medicine, The Mayo Clinic.  
‡Now residing in Ottawa, Canada. Fellow in Medicine, The Mayo Foundation.  
Submitted August 2, 1935.



a clearer idea of its functional capacity may be obtained.

Among the more important and neglected functions of the liver are those which pertain to the detoxification of certain noxious substances. Priestley, Markowitz, and Mann have demonstrated the importance of the liver in these mechanisms, by various experimental procedures. The best known of these detoxifying functions is, as Quick (9) has pointed out, that which is concerned with a conjugation of benzoic acid and glycine to form hippuric acid. Bryan was one of the first to note that hepatic disease might affect the rate of synthesis of hippuric acid, but present interest in the study of this function is the result of the work of Quick (9, 10). It was at his suggestion that the test was applied to a study of our clinical material, and an attempt made to correlate the results with other functional tests and the condition of the liver, as noted at necropsy or operation.

The site of synthesis of hippuric acid has been the subject of much debate; this matter is considered in detail in Bryan's earlier paper; Bunge and Schmiedeburg originally claimed that in the dog it was effected by the kidney and later experiments have corroborated this fact (8). Subsequent studies have shown that in the rabbit (3) and possibly in the human (7), the liver may be the principal site of formation of hippuric acid (3). Quick (7) has demonstrated that the rate of formation of hippuric acid depends to a large extent on the speed at which glycine can be furnished. In other words, the amount of hippuric acid formed does not depend so much on the amount of benzoic acid given as on the rate of formation of glycine. It has been generally supposed that the latter substance is formed by the liver and that in hepatic disease the glycine available for purposes of synthesis is reduced. It was on this basis that the hippuric acid test of hepatic function was advanced. Quick (9) has published the results of a series of cases studied by this means and his results seem to indicate the probable usefulness of the method in clinical practice.

#### METHODS

The methods used by us are those recommended by Quick (8) and for details the reader is referred to his original article. The test is performed by administering, by mouth, 6 gm. of sodium benzoate dissolved in a small amount of water; this may be given after a breakfast of coffee and toast, and should be followed by the administration of a half glass of water. The patient is instructed to void immediately after taking the drug, and hourly specimens of urine are collected for four hours thereafter. Hippuric acid is determined by a simple gravimetric method, the hippuric acid being precipitated by acidification with concentrated hydrochloric acid. If the volume of the individual specimen is large, it should be concentrated to about 50 c.c. by boiling. The specimen is allowed to stand until precipitation is complete and is then filtered; the filtrate is washed with cold distilled water and allowed to dry. The filtrate is then weighed and to the observed weight of hippuric acid is added a correction to allow for the quantity remaining dissolved in the urine. This is necessary since 100 c.c. of urine will hold 0.33 gm. of hippuric acid in solution. The results are best expressed in terms of benzoic acid, which can be determined by multiplying the amount of hippuric acid by the factor 0.68. We have used the total four-hour output as the figure indicating the completeness of the synthesis of hippuric acid.

Quick recommended separate determinations of hippuric acid in each of the four specimens obtained hourly, especially in cases in which any doubt exists in regard to gastric retention; if the accuracy of the collection of urine is in doubt, this also may be the safest procedure.

If more accurate determinations are required, the specimens of urine may be extracted with ether, hydrolyzed with hydrochloric acid, and the glycine thus liberated determined by titration with formol. For clinical purposes, the simple gravimetric method seems sufficiently accurate. The excretion of benzoic acid in normal subjects varies but is usually about 3 gm. under the conditions of the test. It has been pointed out that in actual practice the range of excretion is from 85 to 110 per cent of this amount (2.55 to 3.3 gm.). In eleven hospital patients, presumably without hepatic involvement, which we studied (duodenal ulcer, neurosis, arthritis, chronic cholecystitis, pernicious anemia), the results fell within this range in all but two cases. In one case in which there was functional vomiting, and in another case in which there was duodenal ulcer, figures 0.15 gm. below the lower limits of normal were noted. These were perhaps explainable on the basis of delayed absorption, dehydration, and malnutrition.

In view of the earlier experience of Bryan, who demonstrated that the elimination of hippuric acid was altered in various types of nephritis and other conditions associated with renal involvement, it was obvious that some attention had to be paid to the presence of disorders of the kidney in attempting to apply the test to studies of hepatic function. Snapper and Grünbaum noted that the elimination of hippuric acid was normal in all types of renal disease, provided there was no retention of urea in the blood; they also showed that if the concentration of urea in the blood was elevated, the rate of elimination of hippuric acid was greatly decreased. Bryan's studies gave somewhat similar results. For practical purposes, therefore, it is desirable to confine the use of the test to cases in which the amount of urea in the blood is within normal limits. Snapper and Grünbaum also contended that there was some relation between elimination of water and elimination of hippuric acid, and it is quite probable that erroneously low values for the elimination of hippuric acid may be obtained in cases in which the patients are dehydrated and secrete a small amount of urine.

#### MATERIAL

We have studied the excretion of hippuric acid of thirty-seven patients who had various types of hepatic disease and have attempted to make comparisons with the results of other hepatic functional tests, with the findings at operation and at necropsy, and with certain clinical factors, such as the general condition of the patient and the severity of postoperative reactions. The results in this small series seem to indicate that the test gives a reasonably satisfactory idea of the general state of the hepatic parenchyma, and, for general clinical purposes, is probably as reliable and satisfactory as any other type of hepatic functional test now in use. Ease of performance and relative specificity also recommend it.

#### PORTAL AND BILIARY CIRRHOSIS; SPLENIC ANEMIA

Twelve patients who had various types of cirrhosis were studied; the results in these cases are tabulated

in Tables I and II. In the three cases of definite portal cirrhosis, there was definite correlation of the hippuric acid test and the observed degree of retention of bromsulphalein. The bromsulphalein test is generally regarded as one of the most satisfactory clinical methods for the determination of hepatic function in cirrhosis, especially if jaundice is absent, as it was in these cases. The correlation of the hippuric acid test and the reversal of the albumin-globulin ratio is also of some interest, especially since it is now believed that this phenomenon is often associated with advanced hepatic damage (Myers and Keefer). The patient with the smallest elimination of hippuric acid had a definite reversal of the albumin-globulin ratio and a reduction in the amount of total protein in the blood serum. The other two patients, who were in considerably better general condition than the previously mentioned patient, had a normal albumin-globulin ratio, although the total amount of serum protein was reduced. In two cases in which there was a very chronic type of syphilitic cirrhosis, the patient with the lowest elimi-

TABLE I

*Results of Laboratory Tests in Cases of Cirrhosis, Without Jaundice*

| Case                          | Benzole acid, gm. | Serum bilirubin, mg. per 100 c.c.; van den Berg's reaction | Dye retention, grade | Serum protein, mg. per 100 c.c. | Albumin-globulin ratio |
|-------------------------------|-------------------|------------------------------------------------------------|----------------------|---------------------------------|------------------------|
| Portal cirrhosis, ascites     |                   |                                                            |                      |                                 |                        |
| 1                             | 1.60              | 2.0 direct                                                 | 4                    | 5.80                            | 1.00:1.2               |
| 2                             | 1.75              | 2.0 direct                                                 | 3                    | 5.24                            | 2.73:1.0               |
| 3                             | 2.30              | 1.0 indirect                                               | 2                    | 4.67                            | 2.60:1.0               |
| Syphilitic cirrhosis, ascites |                   |                                                            |                      |                                 |                        |
| 4                             | 1.10              | 1.9 direct                                                 | 3                    | 6.50                            | 1.00:1.3               |
| 5                             | 1.56              | —                                                          | 4                    | 4.99                            | 1.50:1.0               |
| Splenic anemia with cirrhosis |                   |                                                            |                      |                                 |                        |
| 6                             | 2.07              | 3.5 direct                                                 | 3                    | 6.20                            | 1.00:1.8               |
| 7                             | 2.47              | 1.8 direct                                                 | 3                    | 4.87                            | 1.89:1.0               |

nation of hippuric acid showed reversal of the albumin-globulin ratio.

In two cases of splenic anemia and cirrhosis, the hippuric acid test gave results which were nearly normal. The second patient had had splenectomy performed a year previously and had made a satisfactory recovery, in spite of the presence of marked cirrhosis, which was verified at operation. In this case the hippuric acid gave practically normal results. In the other case, in which there was definite jaundice and a reversal of the albumin-globulin ratio, the synthesis of hippuric acid was reduced, a point which seemed to agree with the acuity of the process and the probable degree of hepatic damage.

Three patients who had chronic diffuse hepatitis and jaundice of the type usually described as biliary cirrhosis were studied. In these cases, as will be noted from Table II, there was a fairly close correlation of the rate of synthesis of hippuric acid and the excretion of galactose. The hippuric acid test also checked fairly well with the general clinical condition of the three patients; the most marked reductions in synthe-

sis of hippuric acid were noted in the two cases in which the lesions were more chronic and extensive. A still more striking correlation was noted in the two

TABLE II

*Results of Laboratory Tests in Cases of Chronic Diffuse Hepatitis With Jaundice (Biliary Cirrhosis)*

| Case            | Benzole acid, gm. | Serum bilirubin, mg. per 100 c.c. | Dye retention, grade | Galactose tolerance test, gm. | Serum protein, mg. per 100 c.c. | Albumin-globulin ratio |
|-----------------|-------------------|-----------------------------------|----------------------|-------------------------------|---------------------------------|------------------------|
| 8               | 1.48              | 2.0                               | 3                    | 2.41                          | 8.08                            | 1:1.6                  |
| 9               | 1.65              | 11.0                              | —                    | 1.24                          | 5.60                            | 1:2.0                  |
| 10              | 1.95              | 5.0                               | 4                    | 0                             | 8.77                            | 1:1.1                  |
| Chronic atrophy |                   |                                   |                      |                               |                                 |                        |
| 11              | 0.47              | 15.0                              | —                    | 4.16                          | 6.40                            | 1:1.4                  |
| 12              | 0.28              | 10.0                              | —                    | 3.93                          | 7.86                            | 1:2.32                 |

cases listed under the heading of chronic atrophy (Table II), which was the diagnosis at necropsy. The hippuric acid test, performed in each case shortly before the appearance of fatal hepatic insufficiency, was strongly positive; in each case, a positive galactose test, a marked serum bilirubinemia, and a reversal of the albumin-globulin ratio were also observed. In Case 11, the liver weighed 785 gm.; in Case 12, it weighed 1,553 gm. In both cases, extreme atrophy of the hepatic parenchyma was noted, and there were practically no regenerative changes. Careful examination of the kidneys in each instance failed to reveal any evidence of renal damage which could have affected the tests in question.

#### INTRAHEPATIC JAUNDICE

Six patients (Table III) who had intrahepatic jaundice were studied, the two most interesting being

TABLE III

*Results of Laboratory Tests in Cases of Intrahepatic Jaundice*

| Case | Benzole acid, gm. | Galactose tolerance test, gm. | Serum bilirubin, mg. per 100 c.c. | Remarks                                 |
|------|-------------------|-------------------------------|-----------------------------------|-----------------------------------------|
| 13   | 0.73              | 9.01                          | 20.8                              | Severe cinchophen hepatitis             |
| 14   | 2.65              | 3.80                          | 3.4                               | Cinchophen hepatitis, stage of recovery |
| 15   | 0.90              | 3.00                          | 15.6                              | Severe epidemic (?) jaundice            |
| 16   | 1.74              | —                             | 4.5                               | Epidemic jaundice                       |
| 17   | 2.60              | 0                             | 3.6                               | Epidemic jaundice, stage of recovery    |
| 18   | 3.07              | 1.77                          | 10.1                              | Epidemic jaundice, stage of recovery    |

individuals who had hepatitis, which presumably had been caused by cinchophen. The first patient (Case 13) was acutely ill; the value for the serum bilirubin

was 20 mg., and the excretion of galactose was 9 gm. in five hours. The very low elimination of hippuric acid in this case corresponded with the probable degree of damage to the liver. The second patient (Case

TABLE IV

*Results of Laboratory Tests in Cases of Cholecystitis, Cholelithiasis, and Associated Hepatitis*

| Case | Benzole acid test, gm. | Serum bilirubin, mg. per 100 c.c.; van den Bergh's reaction | Galactose tolerance test, gm. | Remarks                          |
|------|------------------------|-------------------------------------------------------------|-------------------------------|----------------------------------|
| 19   | 0.72                   | 11.3 direct                                                 | 4.70                          | Unusually severe hepatitis       |
| 20   | 1.48                   | 1.2 direct                                                  | 0                             | Postoperative colic              |
| 21   | 1.85                   | 24.2 direct                                                 | 0                             | Severe cholangitis and hepatitis |
| 22   | 2.09                   | 1.3 direct                                                  | 0                             |                                  |
| 23   | 2.11                   | 4.2 direct                                                  | 1.31                          |                                  |
| 24   | 2.18                   | 5.0 direct                                                  |                               |                                  |
| 25   | 3.18                   | 4.7 direct                                                  |                               | Moderate hepatitis               |
| 26   | 3.60                   | 1.2 indirect                                                |                               | Mild hepatitis                   |

14), who was in a convalescent stage, had an increased excretion of hippuric acid. The galactose test was still weakly positive, but the jaundice had practically disappeared. An increased rate of synthesis of hippuric acid has been noted by Quick in other cases during the convalescent stages of intrahepatic jaundice; this appears to correspond with the increased excretion of phenolsulphonethalein during recovery from acute nephritis.

Of the four cases of epidemic jaundice (Table III) which were studied, the synthesis of hippuric acid appeared to be normal in two, a fact which checked very well with the rapid improvement which was taking place in these cases at the time of observation. The strongly positive hippuric acid test in one case coincided with the severity of the illness and its long duration; in fact, it was at one time believed that the patient (Case 15) was suffering from subacute yellow atrophy. In the whole group of cases of intrahepatic jaundice, the hippuric acid test seemed to give a fair idea of the severity of the hepatic lesion. It will be noted that in three of the four cases, the amount of hippuric acid eliminated paralleled the degree of bilirubinemia observed. In Case 18, the bilirubinemia was rapidly decreasing and the liver was probably in the stage of regeneration.

#### HEPATITIS AND CHOLANGEITIS ASSOCIATED WITH CHOLECYSTIC DISEASE

Twenty cases of so-called surgical types of jaundice (Tables IV and V) were studied with particular care, since in this field any test which gave even an approximate indication of the degree of hepatic injury would be of considerable clinical value in determining surgical risk. Eight of the patients had cholecystic disease with or without stones, associated with hepatitis and cholangitis of various degrees. The diagnosis was verified surgically in each case, and since the common bile duct contained no stones in any case it was assumed that the jaundice was not of a def-

ninitely obstructive type. In six of these cases the hippuric test was positive. In Case 19, which presented the greatest impairment of synthesis of hippuric acid, the patient was acutely ill; the value for the serum bilirubin was 11.3 mg. and the excretion of galactose was 4.7 gm. in five hours. An unusually extensive hepatitis was noted at operation; the postoperative course was very stormy, and the convalescence prolonged. In another case (Case 21) the galactose test was negative, although the patient was deeply jaundiced and acutely ill. At operation, all of the extrahepatic biliary passages showed evidence of marked infection, and the hepatic parenchyma was severely damaged. The second patient listed in Table IV (Case 20) had a postoperative cholangitis with biliary colic; the exact state of the liver had not been verified at operation when the hippuric acid test was performed. In the remaining five cases of this group, the elimination of hippuric acid was 2 gm. or more, and mild to moderate degrees of hepatitis were noted at operation.

Of the twelve cases of obstructive jaundice pre-

TABLE V

*Results of Laboratory Tests in Cases of Obstructive Jaundice*

| Cause of obstruction | Case | Benzole acid test, gm. | Serum bilirubin, mg. per 100 c.c. | Dye retention, grade | Galactose tolerance test, gm. | Remarks                                                                      |
|----------------------|------|------------------------|-----------------------------------|----------------------|-------------------------------|------------------------------------------------------------------------------|
| Stone                | 27   | 0.00                   | 12.0                              |                      | 0                             | Stone in common bile duct; patient jaundiced one year and in poor condition. |
|                      | 28   | 2.09                   | 2.0                               | 3                    |                               | Stone in common bile duct; recent colic.                                     |
|                      | 29   | 3.10                   | 1.5                               |                      | 0                             | Stone in common bile duct; marked hepatitis; patient convalescing.           |
| Stricture            | 30   | 1.30                   | 3.5                               | 1                    | 3.00                          | Stricture of common bile duct; biliary cirrhosis.                            |
|                      | 31   | 1.58                   | 5.8                               |                      | 5.31                          | Stricture of common bile duct; biliary cirrhosis; external biliary fistula.  |
|                      | 32   | 1.83                   | 7.5                               |                      | 2.10                          | Stricture of common bile duct; biliary cirrhosis.                            |
|                      | 33   | 2.20                   | 3.1                               |                      | 0                             | Stricture of common bile duct                                                |
| Carcinoma            | 34   | 0.50                   | 12.5                              |                      | 0                             | Carcinoma of pancreas; marked cirrhosis.                                     |
|                      | 35   | 0.52                   | 22.1                              |                      |                               | Carcinoma of ampulla of Vater; marked cirrhosis.                             |
|                      | 36   | 2.45                   | 14.6                              |                      | 0                             | Carcinoma of pancreas; hepatitis and cholangitis.                            |
|                      | 37   | 2.65                   | 12.3                              |                      | 0                             | Carcinoma of pancreas; liver in fair condition.                              |
|                      | 38   | 2.90                   | 3.5                               | 2                    |                               | Carcinoma of pancreas (early).                                               |

sented in Table V, three deserve particular comment. In the first (Case 27), the excretion of hippuric acid was nil, except for the amount remaining in solution in the urine. This patient had had repeated attacks of

biliary colic and had been jaundiced continuously for more than a year. She was very anemic and in extremely poor condition. It will be noted that the galactose test was negative in this case, and it is believed that a much more accurate idea of the degree of hepatic damage present was obtained from the hippuric acid test. In all of the cases in which there was a stricture of the common bile duct and definite biliary cirrhosis, the hippuric acid test was positive; the lowest rates of synthesis were noted in the two cases in which the patients were in the poorest condition from the clinical standpoint. In both of these cases the rate of excretion of galactose was somewhat greater than normal. In two of the five cases in which carcinoma occluded the biliary passages (Cases 34 and 35), the hippuric acid test was strongly positive, and in each instance it was noted at operation that the degree of hepatic damage was extreme. In these cases, hepatic insufficiency and death ensued shortly after operation. A misleading result was obtained in the third case of the group (Case 36), in which the hippuric acid test gave an approximately normal result. The patient gave an antecedent history of chills and fever; marked hepatitis and suppurative cholangitis were noted at operation and later were verified at necropsy. After consideration of the postmortem findings, it seemed fair to assume that the hepatic damage present was the result of the infectious process and was not caused by the damage which had occurred directly as a result of biliary obstruction. Nevertheless, a positive hippuric acid test would have been expected, since the degree of hepatic destruction was considerable.

In the whole group of patients who had "surgical types" of jaundice, the rate of synthesis of hippuric acid could be correlated well with the observed degree of hepatic injury, the general clinical condition of the patient, and the degree of postoperative reaction. Vaccaro (12) has also studied the rate of synthesis in a similar series of cases and his conclusions were similar to ours. From a consideration of Tables IV and V, it will be noted that there was little if any correlation of the excretion of galactose and the synthesis of hippuric acid. However, general agreement between the degree of bilirubinemia and the rate of hippuric acid synthesis was noted. In the whole series of cases, it appeared that the hippuric acid test gave a reasonably good idea of the actual state of the liver and its ability to withstand surgical procedures. We believe that in cases in which the elimination of hippuric acid is 1.5 gm. or less, severe damage of the hepatic parenchyma can be assumed to exist, and that surgical procedures will entail a considerably increased risk. On the basis of the one case previously mentioned, it seems that a negative hippuric test probably does not entirely exclude a critically damaged liver. It should be noted that the test does not differentiate obstructive and intrahepatic jaundice; in fact, there are theoretical reasons to believe that no test will ever accomplish this differentiation with any great degree of accuracy. The peculiar merit of the test lies in the fact that it gives satisfactory results in jaundiced patients; where the dye tests cannot be used satisfactorily, and that in the

nonicteric patient, in which the galactose test is of little value, the hippuric acid test appears to give accurate information.

In the foregoing paragraphs, we have laid particular emphasis on the frequency with which the results of the hippuric acid test correspond with the results of other tests of hepatic function and also with the condition of the liver, as noted by the surgeon at operation. Cases in which no such correlation existed should also be mentioned. The relatively small elimination of hippuric acid in two cases in which the livers presumably were normal and the case of malignant obstruction of the biliary passages and suppurative cholangitis (Case 36) in which the elimination of hippuric acid was normal have been mentioned previously. Two other cases were encountered in which the test gave results which we believe to be misleading. In one case in which extensive metastatic carcinoma of the liver was verified at operation, there was a normal synthesis (3.3 gm.). In another case in which there was a pyogenic granuloma in the subdiaphragmatic space, two hippuric acid tests gave strongly positive results, the total urinary output (calculated as benzoic acid) in each case was approximately 1.2 gm. At necropsy, no hepatic lesion could be found which in any way explained this finding. In other words, there is probably a definite margin of both negative and positive error in the use of this test. We know of no hepatic functional test, however, of which this same statement cannot be made, and the statement does not imply a serious criticism of any test. As Mann has pointed out, some general reservations must be made in interpreting the results of tests of hepatic detoxification. It has not yet been conclusively demonstrated that the liver is the sole site of synthesis of hippuric acid in the human subject; neither has the test been studied in relation to the physiologic state of the liver at the time the test substance is administered. It would also appear desirable to have more information in regard to the rate of elimination of hippuric acid in the so-called toxic nephroses, which are not uncommonly present in association with hepatic injury. From a practical (and perhaps an empiric) standpoint, the test seems to give information of clinical value, in spite of some objections based on physiologic grounds.

#### SUMMARY AND CONCLUSIONS

In a series of thirty-eight patients who had various types of hepatic disease, the results of the hippuric acid test for hepatic function were studied in an attempt to correlate the results of such generally used procedures as the bromsulphalein test and those of the galactose test. The results seem to indicate that the rate of synthesis of hippuric acid is a reasonably accurate and satisfactory test for the determination of parenchymatous hepatic damage, particularly in the "surgical" types of jaundice. The errors noted are no greater than are those to which other hepatic functional tests are subject. From a physiologic standpoint, these results are of interest, since they add to the accumulated evidence which indicates that hepatic lesions have a definite influence on the rate of synthesis of hippuric acid in human beings.

## REFERENCES

1. Bryan, A. W.: Clinical and experimental studies on sodium benzoate; the value of the sodium benzoate test of renal function and the effect of injury of the liver on hippuric acid synthesis. *Jour. Clin. Invest.*, 2:1-33, Oct., 1925.
2. Bunge, G., and Schmiedeberg, O.: Ueber die Bildung der Hippursäure. *Arch. f. exper. Path. u. Pharmacol.*, 6:233-255, Nov. 17, 1877.
3. Friedmann, E., and Tachau, Hermann: Über die Bildung des Glykokolls in Tierkörper. I. Synthese der Hippursäure in der Kaninchenleber. *Biochem. Ztschr.*, 35:88-103, 1911.
4. Mann, F. C.: Hepatic function in relation to hepatic pathology: experimental observations. *Ann. Int. Med.*, 8:432-443, Oct., 1934.
5. Myers, W. K., and Keefer, C. S.: Relation of plasma proteins to ascites and edema in cirrhosis of the liver. *Arch. Int. Med.*, 55:349-359, March, 1935.
6. Priestley, J. T., Markowitz, J., and Mann, F. C.: Studies on the physiology of the liver. XX. The detoxicating function of the liver with special reference to strychnine. *Am. Jour. Physiol.*, 96:696-703, March, 1931.
7. Quick, A. J.: The conjugation of benzoic acid in man. *Jour. Biol. Chem.*, 92:65-85, June, 1931.
8. Quick, A. J.: The site of the synthesis of hippuric acid and phenylacetic acid in the dog. *Jour. Biol. Chem.*, 96:73-81, April, 1932.
9. Quick, A. J.: The synthesis of hippuric acid: a new test of liver function. *Am. Jour. Med. Sc.*, 185:630-636, May, 1933.
10. Quick, A. J.: Personal communication to the authors.
11. Snapper, J., and Grünbaum, A.: Der Hippursäure-Stoffwechsel bei Nierenkrankheiten. *Klin. Wchnschr.*, 3:101-104, Jan. 15, 1924.
12. Vaccaro, P. F.: The synthesis of hippuric acid; its value in detecting hepatic damage secondary to diseases of the extrahepatic biliary system. *S., G., and O.*, 61:36-42, July, 1935.

## Phenolphthalein Studies\*

## I. Colloidal Phenolphthalein

By

BERNARD FANTUS, M.D.

and

J. M. DYNIEWICZ

CHICAGO, ILLINOIS

IT seems that a stable colloidal phenolphthalein preparation is not as yet available. Inasmuch as it may be reasonably assumed that such colloidal phenolphthalein would have a higher degree of solubility than the highly insoluble crystalline form, we have undertaken experiments to determine whether such a preparation might be developed.

The nearest approach to a colloidal phenolphthalein seems to have been secured by E. B. Putt (1) who obtained a patent upon the microcrystalline form (Brit. Pat. 352,924, April 4, 1930, and U. S. A. Pat. No. 1574934 and 1693666) with the claim that he had produced a "finely divided crystalline phenolphthalein obtained by pptg. an alk. solu. of phtn. with an acid in the presence of a colloid such as gum acacia or tragacanth or agar agar, sufficient to delay pptn. but insufficient to form a thick gel. on standing. HoAc may be used for the pptn."

There is no doubt that Putt secured a colloidal solution of phenolphthalein; but this does not remain colloidal for more than a very short time. He did not solve the problem of colloidal phenolphthalein in stable solid or liquid form.

The colloidal solution of phenolphthalein produced by precipitating the phenolphthalein by means of acetic acid in the presence of either 1% tragacanth or 1% agar or 1% acacia, as undertaken by Putt, does not remain colloidal for more than a very short time.

We have attempted to prepare colloidal phenolphthalein by passing a stream of carbon dioxide gas over a solution made by dissolving 1 gm. phenolphthalein in 50 c.c. N/10 NaOH and then made up to 100 c.c. with distilled water so as to represent a 1% solution of phenolphthalein. As this process yields a white milky fluid, containing microcrystalline phenol-

phthalein, which soon sediments the phenolphthalein in crystalline form, we added various "protective colloids," such as gelatin, bile, bile salts (sodium taurocholate, sodium glycocholate and "decholin" sodium), and saponin to the solution. Carbon dioxide gas was then passed over the surface of the liquid with constant agitation until the color was discharged. The result is an opalescent fluid that on standing gradually becomes a milky white and ultimately yields a white sediment of crystalline phenolphthalein: the time relations depending somewhat upon the proportion and nature of the protective colloid.

**Solubility of Colloidal Phenolphthalein.** The solubility of the colloidal phenolphthalein thus obtained, in comparison with the crystalline phenolphthalein, is shown in the subjoined table (Table I), as far as expression of color permits.

TABLE I

|                                    | pH— | 7.8 | 8.0  | 8.2 | 8.4  | 8.6 | 8.8  |
|------------------------------------|-----|-----|------|-----|------|-----|------|
| White Phenolphthalein              |     | 0   | 0    | 0   | tr.  | tr. | tr.+ |
| Yellow Phenolphthalein             |     | 0   | 0    | 0   | tr.  | tr. | tr.+ |
| Mic. Cryst. Phenolphthalein        |     | 0   | 0    | 0   | tr.  | tr. | tr.+ |
| Coll. Phtn. 1% Gel.                | ?   | tr. | tr.+ | +   | ++   | +++ | +++  |
| Coll. Phtn. 1% Decholin Sodium     | ?   | tr. | tr.+ | +   | ++   | +++ | +++  |
| Coll. Phtn. 1% Bile                | ?   | tr. | tr.+ | +   | ++   | +++ | +++  |
| Coll. Phtn. 1% Sodium Taurocholate | ?   | tr. | tr.+ | +   | ++   | +++ | +++  |
| Coll. Phtn. 1% Sodium Glycocholate | ?   | tr. | tr.+ | +   | ++   | +++ | +++  |
| Coll. Phtn. 1% Saponin             | ?   | tr. | tr.+ | +   | ++   | +++ | +++  |
| Coll. Phtn. 0.3% Saponin           | ?   | tr. | tr.+ | +   | ++   | +++ | +++  |
| Coll. Phtn. 0.1% Saponin           | 0   | 0   | tr.  | tr. | tr.+ | +   | +    |
| Coll. Phtn. 1% Tragacanth          | ?   | tr. | tr.+ | +   | ++   | +++ | +++  |
| Coll. Phtn. 1% Acacia              | ?   | tr. | tr.+ | +   | ++   | +++ | +++  |
| Coll. Phtn. 1% Agar                | ?   | tr. | tr.+ | +   | ++   | +++ | +++  |

It is also shown by line 3 (Fig. 1). The lines 1 and 2 of Figure 1 were obtained by occasional agitation for one hour, filtration, and mixing the filtrate with an equal volume of N/10 NaOH V.S., to bring out the pink color to its maximum value, and then estimating the quantity in solution by means of a colorimeter. Line 1 represents solubility at room temperature (25° C.), line 2 at body temperature (38° to 40° C.). Line 3 was obtained in a manner somewhat different from

\*From the Laboratory of Pharmacology and Therapeutics of the College of Medicine, University of Illinois, and assisted by a grant from Phenolphthalein Research, Inc.  
Submitted November 2, 1935.  
(1) *Chem. Abst.*, 26:5315 (1932).



the one that was used in developing curves 1 and 2, because of the impossibility of filtering the colloidal solution. We therefore estimated the amount of dissolved phenolphthalein by a direct matching of color as compared with an alcoholic standard solution of

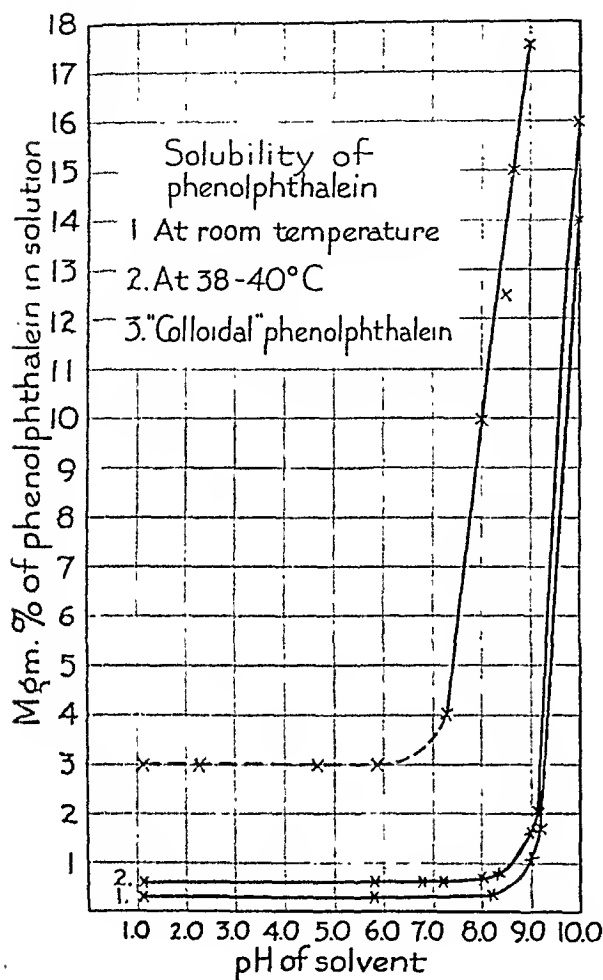


Fig. 1

phenolphthalein added to fluid of the same pH. The broken portion of line 3 indicates that below pH 8.0 there is practically no color. Diffusion experiments (the results of which are represented by the broken line) indicate that a considerably greater quantity goes into solution even below this point in pH value than is the case with crystalline phenolphthalein.

**Preparation of Colloidal Phenolphthalein.** We believe we have succeeded in producing a stable "colloidal" phenolphthalein in solid form by the following process:

|                  |            |
|------------------|------------|
| Citric acid      | 1.0 Gm.    |
| Phenolphthalein  | 2.15 Gm.   |
| Granular gelatin | 5.0 Gm.    |
| N 1 NaOH V.S.    | 10.75 c.c. |
| Distilled water  | 50.0 c.c.  |

The phenolphthalein is dissolved in the N 1 NaOH V.S. with the aid of heat and is filtered through paper. The gelatin is dissolved in the distilled water with the aid of gentle heat. The two solutions are mixed. A stream of CO<sub>2</sub> gas is passed with agitation over the

surface of the solution contained in a relatively large Erlenmeyer flask until the color is completely discharged. Finally, the citric acid is added, until a pH of 5.5 is obtained. The resulting mixture is spread in a thin sheet on glass plates and dried at room temperature.

An explanation of the reason for each of the ingredients and of the process as a whole might be desirable.

Phenolphthalein sodium is produced in the first step by dissolving the phenolphthalein in the sodium hydroxide solution. This results in a red liquid. Gelatin is used because it has been found to be the most potent "protective" colloid. The more distant the particles are from each other, in other words, the more dilute the solution, the finer the precipitate. Hence, carbonic acid, one of the feeblest of acids, is employed; and we get a better colloid if we merely pass the gas over the surface of the solution than when we permit it to bubble through. The exposure to CO<sub>2</sub> is continued with gentle agitation until the pink color is lost completely. We then know that the sodium salt has been decomposed. A yellowish opalescent fluid is the result. As, in spite of all these precautions, the particles coalesce when the preparation is kept in the liquid state, and larger aggregates form and a precipitate occurs, we proceeded to dry the product. To be able to do this, it was necessary to add a non-volatile acid, such as citric acid, as otherwise during the drying the CO<sub>2</sub> would be lost and the product return to the original pink color of the phenolphthalein sodium. The resulting scales contain about 25 per cent of phenolphthalein.

It is possible to make a product as strong in phenolphthalein as 33 per cent, but not much stronger.

**Physical characteristics:** The material occurs in glistening yellowish scales that should be quite transparent and no more than slightly opalescent, odorless, and have a rather persistently bitter taste.

#### TESTS FOR COLLOIDAL PHENOLPHTHALEIN

That we have produced a phenolphthalein of a much higher solubility rate than the ordinary form may be proved by the following tests:

1. The finely powdered material strikes a pink color immediately with a buffer solution of pH 8.2 at 40° C.
2. Sodium bicarbonate solution (pH 8.0) strikes no color with crystalline phenolphthalein, but is colored pink by colloidal phenolphthalein. This difference is better shown when the product is freshly prepared. The dry material needs to be dissolved in a little water with the aid of gentle heat (not above 40° C.).

It might be inserted here parenthetically that, when phenolphthalein is used as indicator, i.e., when one puts several drops of 1% alcoholic solution of phenolphthalein into sodium bicarbonate solution, a pink color is obtained. The reaction is dependent upon what we believe to be the colloidal condition; for this reaction could not be obtained unless the phenolphthalein test solution (in alcohol) is used. The rather large quantity of phenolphthalein required has been ascribed to mass action (cf. *Chem. Abstr.*, 18:2788, 1924); but it certainly must also be due to colloidal condition of the precipitate for no color change occurs when even a large excess of crystalline phenolphthalein is added to the bicarbonate solution, unless the solution is permitted to stand, when—on account of loss of CO<sub>2</sub>—a higher pH value and solution of the phenolphthalein result.

3. The difference between a solution of crystalline phenolphthalein and of colloidal phenolphthalein in sodium bicarbonate solution can also be brought out by instillation of such solutions into the human conjunctiva. We prepared a 2.12% solution of sodium bicarbonate, which is isotonic with the tears and has a pH of 8.0. We saturated this with crystalline phenolphthalein and another portion of such solution with colloidal phenolphthalein. It is im-





Fig. 2

possible to distinguish, after instillation in the conjunctiva, between crystalline phenolphthalein solution and the bicarbonate solution without phenolphthalein. The solution of the colloidal phenolphthalein, which is pink in contrast with the colorless solution of the crystalline form, causes a smarting sensation in the conjunctiva that lasts for a few minutes.

4. The taste of colloidal phenolphthalein is decidedly bitter, unless the mouth is quite acid, as it may be the first thing in the morning. There is practically no taste sensation produced by crystalline phenolphthalein.

5. The microscope shows very few of the characteristic crystals of phenolphthalein (Fig. 2) in a good preparation of colloidal phenolphthalein (Fig. 3).

*Quantitative estimation:* The scales should contain about 25 per cent of colloidal phenolphthalein and not less than 23 per cent or more than 25 per cent, which may be tested for as follows:

Place 0.010 Gm., accurately weighed, of the material to be tested in a 50 c.c. glass stoppered, graduated cylinder; add 50 c.c. of a buffer solution pH 8.2 at a temperature of 40° C.; and maintain this temperature until all is dissolved and the maximum color is reached. At the same time, heat another 50 c.c. of buffer solution and add an alcoholic standard solution of phenolphthalein (containing 0.5 Gm. in 100 c.c. of alcohol) until the color matches that produced by the material to be assayed, using a colorimeter for the final comparison.

From the amount of standard phenolphthalein solution used, the per cent of colloidal phenolphthalein may be determined.

When crystalline phenolphthalein is treated in the same way, it does not yield more than about 4 per cent of phenolphthalein to a solution at this pH.

#### SAPONIN STABILIZED COLLOIDOL PHENOLPHTHALEIN

There is one way we have been able to secure a relatively stable colloidal phenolphthalein in liquid form; and that is by means of saponin.

When one adds to a one per cent solution of phenolphthalein in 50 c.c. of N/10 sodium hydroxide solution, ½ per cent of saponin and passes a stream of carbon dioxide over the solution, a white milky fluid results, which, on standing in a refrigerator, deposits a sediment, leaving, however, a milky supernatant fluid. This supernatant

fluid, after prolonged standing (about two months), has been found to contain phenolphthalein, soluble in pH 8.2; and, assayed as above described, it was found to contain 41 per cent of the phenolphthalein still in colloidal form.

*Fate of Colloidal Phenolphthalein in Artificial Gastric Juice.* It becomes of interest to determine what happens to colloidal phenolphthalein when it passes through the stomach. We therefore incubated (at 38°-40° C.) colloidal phenolphthalein with artificial gastric juice prepared according to the following formula:

|               |            |
|---------------|------------|
| Pepsin        | 1.5 Gm.    |
| N/10 HCl V.S. | 100.0 c.c. |

This solution (with the colloidal phenolphthalein added) has a pH of 1.1, which might be considered a relatively high degree of gastric acidity and a rather severe test for the stability of our colloid in the stomach. We find that our bicarbonate solution test for phenolphthalein colloid can be obtained up to but not after half hour's incubation at the pH of 1.1. At a lower pH, however, the test can be secured for a much longer time,—up to two hours (Table II).

TABLE II

| Incubation (38°-40° C.) of colloidal phenolphthalein at pH: |       |       |        |
|-------------------------------------------------------------|-------|-------|--------|
|                                                             | 1.1   | 1.5   | 2.5    |
| Colloid absent after                                        | ½ hr. | 1 hr. | 2 hrs. |

*Purgative Value of Colloidal Phenolphthalein.* In view of the greater solubility of colloidal phenolphthalein, one might expect it to have a greater degree of purgative action. A fairly well controlled study in a small group (24 persons) showed that it does indeed possess greater potency than the U.S.P. phenolphthalein, but that it is probably not more than twice as active. There is a possibility that it may be more uniformly active than the crystalline form. This remains to be shown.

The disadvantage of colloidal phenolphthalein is its bitter taste, which would demand administration in capsule form.

#### Colloidal Phenolphthalein in Petrolatum Emulsions.

In view of the fact that there is a tendency to separation of phenolphthalein on prolonged standing in emulsions of liquid petrolatum containing phenolphthalein, it seemed of interest to determine whether col-

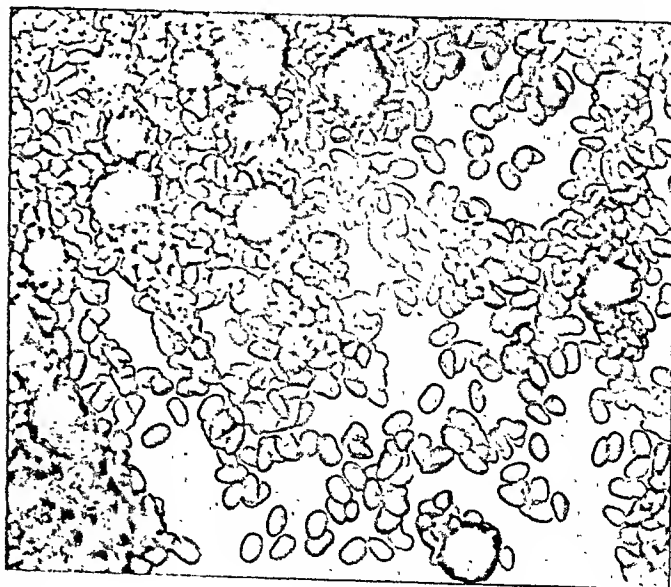


Fig. 3

loidal phenolphthalein could be incorporated in an emulsion and how long it would remain colloidal.

It should be noted here that when, in the making of this preparation, an alcoholic solution is added to the emulsion, a precipitate of colloidal quality is secured. This is shown by the fact that this solution strikes a pink color with buffer solution of pH 8.2. This reaction is lost, however, within two hours, which indicates that the phenolphthalein has lost its colloidal by that time. When we add the gelatin prepared colloidal phenolphthalein to the petrolatum emulsion, the color change is obtained with buffer solution of pH 8.2 for as long as two days, but no longer. It therefore probably presents no practical advantage and has the disadvantage of making the preparation more bitter.

## CONCLUSIONS

1. We have prepared stable colloidal phenolphthalein in solid form.
2. Colloidal phenolphthalein strikes a pink color with sodium bicarbonate solution (pH 8).
3. Colloidal phenolphthalein is considerably more soluble than is crystalline phenolphthalein at the hydrogen ion concentrations prevailing in the human body.
4. Colloidal phenolphthalein has a bitter taste.
5. Colloidal phenolphthalein may pass through the stomach, providing it is not detained in exposure to active gastric juice for an excessive length of time.
6. Colloidal phenolphthalein is somewhat more active in producing bowel evacuation than is the crystalline form.

## ABSTRACTS

W. A. MACKEY.

*Cholecystitis Without Stone. British Jour. Surg., Vol. 22, No. 86, Oct., 1934.*

A detailed investigation is reported of almost 300 operative cases with deductions worthy of merit as to clinical, radiological and pathological aspects. A serious attempt is made to evaluate prognosis. Emphasis is laid particularly on prognosis: is it more favorable in cholelithiasis or in gall bladder disease without stones? Great stress is attached upon evaluation of history, pathological examination and radiological findings.

Although operative mortality has been enormously reduced in recent years, the end results are still not entirely satisfactory. Great significance is ascribed to biliary colics whether functional or organic. It seems that more satisfactory results can be guaranteed from cholecystectomies due to such colics. Moreover this symptom alone is considered of greater importance than the pathological changes themselves.

The Author tried to divide his material into distinctive groups namely gall bladder disease with minimal lesions, chronic catarrhal cholecystitis, chronic fibrous cholecystitis, and cholesterosis of the gall bladder ("strawberry" gall bladder). This classification may fit well practical purposes, histological and roentgenological findings, however, can not be divided so sharply. There still are no decisive histological manifestations of a diseased gall bladder. Clinically only 30% of the cases were cured after cholecystectomies affiliated with stoneless gall bladder disease. About the same amount improved and more than 36% remained unimproved, with an operative mortality of about 3%. It is significant, however, that cases with definite history of biliary colics revealed a much higher percentage of cure following cholecystectomies. Prognostically, therefore cases with colics are easier to cure, although stones may not even be present. Therefore cases presenting biliary colics are an indication for surgery.

Other symptoms such as flatulent dyspepsia, food selection and constipation are only accidental findings, although valuable from practical standpoint. Undoubtedly such symptoms may have their origin outside of the gall bladder.

either in the pylorus or in the colon. Such cases do not respond to cholecystectomies.

An interesting chapter is devoted to the coincidence of appendectomies. It is surprising that appendices were more involved in those cases that have not improved sufficiently. Consequently the removal of the gall bladder was solely responsible for the improvement of the symptoms. Rather poor results were obtained in simple cholesterosis i.e., "Strawberry gall bladder," another point to prove that microscopical changes should not be over-estimated. In more advanced cases of gall bladder disease as chronic fibrous cholecystitis or cholesterosis with stone, the results were better.

Much has been written about pains following cholecystectomies. A disturbed coordination in the activity of the motor elements in the gall bladder, in the sphincter of the gall bladder neck and the sphincter of Oddi were supposed to be responsible for post operative colics and dyspepsias (German view-point). Others thought that accompanying hepatitis, pancreatitis or other functional derangements of the gastro-intestinal tract were to blame for the untoward results. Involvements of accompanying pancreatitis, diminution of HCl secretion and possible derangements of the bile-flow through the common ducts are not mentioned incident to the quite common complaints following surgical procedures on the bile ducts.

The roentgenological findings offer some help. They may be important in establishing a decision for operation. However only in 60% did surgery confirm with the roentgen findings. The only outstanding group was that showing deformed gall bladder shadows. This is practically always a sign of a pathological gall bladder revealing pericholecystitic adhesions. Diminution of intensity or impairment of the density are not sufficient evidences for gall bladder pathology and the same may be said about totally absent gall bladder shadows.

Gall bladder disease without stone is one the border-line between functional and organic disease. All the laboratory methods serve only as helpful hints. Prognosis must be weighed individually based on many of elements entering the complexity of these ailments.

M. E. Gabor, Milwaukee.

## SECTION II—*Experimental Physiology*

### The Influence of Some Organic and Inorganic Acids on the Motility of the Small Intestine\*

By

N. M. GRAY, M.D., M.Sc.  
MONTREAL, CANADA

THAT the contents of the gastro-intestinal tract may influence its neuro-muscular apparatus not only mechanically but also chemically is generally acknowledged. These contents are normally composed of the constituents of the food-stuffs or the products of their disintegration, or the digestive juices themselves. They may influence the motility of the alimentary canal either positively or negatively, that is, they may either stimulate or inhibit intestinal movement. Thus they may rightly be called the "natural chemical stimuli" of the gastro-intestinal tract (Babkin, 1916, 1924, 1925, 1928 (a)).

In the present study only one group of "natural chemical stimuli" was investigated, their effect being tested on the motility of the small intestine of the cat. This group consisted of three acids, namely, hydrochloric acid, lactic acid and acetic acid. The reasons for choosing these particular acids were as follows. *Hydrochloric acid* is a normal product of the secretory activity of the gastric glands. After every meal it passes with the chyme into the duodenum and determines the slightly acid reaction of the duodenal and jejunal contents. The hydrochloric acid has moreover a twofold action on the motility of the small intestine, i.e. partly inhibitory and partly excitatory (Babkin, 1916). This property of hydrochloric acid may provide a clue to the understanding of the changes in the motility of the intestine during the normal course of digestion, for example, when rhythmic segmentation is replaced by a peristaltic wave or by temporary rest of the organ.

The investigation of the excitatory and inhibitory properties of hydrochloric acid may aid us also in understanding some pathological conditions. For instance, in patients with achylia gastrica there is often a tendency to diarrhea owing to the rapid passage of food masses from the stomach to the large intestine; this may be due to the absence of the inhibitory effect of the acid on the motility of the stomach and the faster evacuation of that organ (the "entero-gastric reflex" of Thomas and Morgan, 1931). Another cause of the more rapid transportation of the chyme along the small intestine in cases of achylia gastrica may be

the very weak acid reaction of the chyme, determined probably by organic acids only.

*Lactic acid* was chosen because milk is one of the most generally used food-stuffs. *Acetic acid* is also a very common constituent of foods, being present in vinegars, pickles, etc. However, there is an additional interest in investigating the effect of acetic acid on intestinal motility. According to Magnus (1925) acetylcholine is the substance which stimulates the myenteric plexus, which, in its turn, discharges motor impulses to the intestinal muscles. If this is so, it seems of interest to observe how a loop of intestine will react to a solution of acetic acid introduced into the lumen. If the acid is absorbed by the walls of the loop, might it not convert an inert choline into active acetylcholine? Also, how will physostigmine, which inhibits the effect of the esterase inactivating acetylcholine, change the reaction of the loop to the acid? No complete solution of these complicated problems has been attempted, but a number of definite facts has been accumulated with which to form a basis for later work.

#### EXPERIMENTAL PROCEDURE

As mentioned, the experimental animal employed was the cat. Anesthesia was obtained by intravenous injection of chloralose (0.05 gm. per kilo) and urethane (0.5 gm. per kilo). The vagus nerves were cut on both sides of the neck. The abdomen was opened and the adrenal veins ligated on each side of the adrenal glands, so that the latter were cut off from the general circulation. The splanchnic nerves were then cut on both sides.

The solutions of hydrochloric acid, acetic acid and lactic acid were introduced into the lumen of the gut, for which purpose two denervated loops of small intestine were used. Each loop measured about 10 cm. and in all the experiments at least 15 cm. of intact intestine were left between them. The loops were prepared after the method described by Babkin (1928(b)). At the cephalad end of each loop a straight glass cannula was inserted into the lumen and fixed by a ligature about the mucosa; at the ab-oral end a glass T-piece was similarly inserted and fixed.

When thus prepared, the cat was placed in a bath of Ringer-Locke solution and the lower part of the body submerged to such an extent that the loops were kept constantly 0.5 to 1 cm. below the surface of the solution. The bath was maintained at the cat's body temperature. One limb of the T-piece of each loop was then connected by thin rubber tubing to a Marey's tambour, the other limb being connected to a drain at the side of the tank. The vagi and splanchnic nerves were now sectioned and the

\*From the Department of Physiology, McGill University, Montreal, Canada.  
Submitted July 17, 1935.

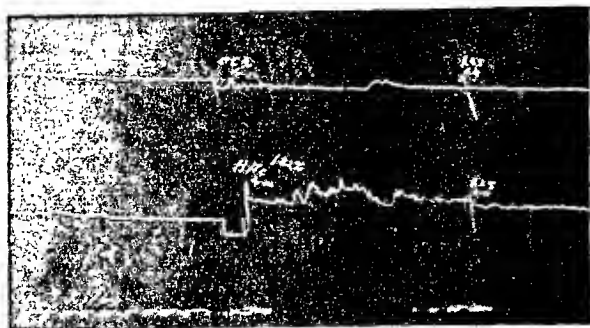


Fig. 1. Cat—wt. 3.0 kgm. Upper tracing—hydrochloric acid 0.00219M. Lower tracing—acetic acid 0.303M.

loops gently washed out with normal saline. After resting the loops for five or ten minutes the experiment would be commenced by filling each loop by means of a pipette with a constant volume of the solution to be tested. Handling of the loops was kept at a minimum.

In some of the experiments rhythmic stimulation of the vagus was carried out, this being obtained by means of an induction coil and a metronome. In these experiments not only was special attention paid to the dissection of the vagi in an effort to preserve their blood supply but the right and left nerves were tested and that producing the greater effect was employed for the experiment.

In all the experiments the solutions of the acids used were made isotonic with blood ( $\Delta .56$ ) by the addition, if necessary, of sodium chloride; their temperature was raised to that of the animal before they were introduced into the loop.

Sufficient experiments were done with the various acids, sometimes in the cephalad and sometimes in the caudad loop, to obviate any false conclusion being drawn as a result of some difference in the activity of the loop depending on its level in the gastro-intestinal tube.

In order to analyse the origin of the effect of the various acids two series of experiments were carried out, namely, Series A and B.

#### SERIES A

In this series the acids all had the same hydrogen ion concentration, equivalent to a pH of 2.5. The pH was checked in all the solutions by means of the hydrogen ion electrode. This particular pH was chosen as being within physiological bounds.

#### SERIES B

In this series only hydrochloric and acetic acids were used. The concentration of the hydrochloric acid was .04 molar, and that of the acetic acid .1 molar. In all the experiments rhythmic stimulation of the vagus was employed.

In both of the above series of experiments the effect of subminimal doses of physostigmine, given intravenously, was noted, and in some experiments this was combined with small doses of eholine hydrochloride, also introduced intravenously.

### EXPERIMENTAL RESULTS

#### SERIES A

In these experiments the acids used were of the same pH but differed in molar concentration. The following table gives their pH, their molar concentration

and the corresponding titratable acidity expressed as a percentage of hydrochloric acid.

|                           | pH  | Molar concentration | Titratable acidity as HCl |
|---------------------------|-----|---------------------|---------------------------|
| Hydrochloric acid (.008%) | 2.5 | .00219              | .008%                     |
| Acetic acid (1.82%)       | 2.5 | .303                | 1.09%                     |
| Lactic acid (.36%)        | 2.5 | .04                 | .146%                     |

As the following graphs will show, acetic acid appeared to be a better stimulant of motor activity than either lactic acid or hydrochloric acid, while lactic acid proved to be superior to hydrochloric acid. Subminimal doses of physostigmine and eholine emphasized the effect of the acids in the same order as that in which they acted alone. Of the many graphs obtained only representative examples are given illustrating the typical responses.

Fig. 1 is from an experiment in which the action of acetic acid and that of hydrochloric acid were compared. The greater effectiveness of acetic acid as a motor stimulant is well shown.

Fig. 2 is from a similar experiment, but here a small dose of physostigmine was administered; the result is a marked accentuation of the superiority of the acetic acid.

Fig. 3 shows two periods during an experiment in which lactic acid and hydrochloric acid were compared. It will be seen that the organic acid caused the greater activity even when, as in the second period, it was placed in the loop which previously held hydrochloric acid. This difference between lactic and hydrochloric acid was accentuated after a small dose of physostigmine.

In numerous experiments acetic acid constantly proved to be a somewhat more effective motor stimulant than lactic acid and this difference was emphasized by physostigmine and choline. Fig. 4 illustrates one such experiment where choline and physostigmine were employed.

#### SERIES B

In these experiments a comparison was made of the effect of hydrochloric acid and acetic acid respectively upon the activity of the intestinal loops, while the loops were undergoing rhythmic stimulation through the vagus. If the modern theory of O. Loewi concerning the chemical transmission of the nerve impulse be accepted, then it is possible that we were superimposing the effect of hydrochloric acid or of acetic acid on that of a local hormone—which might be acetylcholine. Lactic acid was not used. The hydrochloric acid used was .04M with a pH of 1.4, while the acetic acid was .1M with a pH of 2.87.

The results in this series differ somewhat from those in Series A. In some of these experiments the hydrochloric acid solution provoked as good or even slightly better contractions than the acetic acid solution but this was by no means constant. Furthermore the administration of physostigmine seemed to enhance the effect of the acetic acid more than that of the hydrochloric acid.

Fig. 5 is from an experiment in which both eholine and physostigmine were employed. When the loops were first filled with the acids, the activity was about equal in both; if anything, the loop containing hydrochloric acid was a little more active, and it will be seen that the first dose of eholine hydrochloride (2 mgm.) produced an approximately equal effect on the two loops. After six minutes the dose of choline was

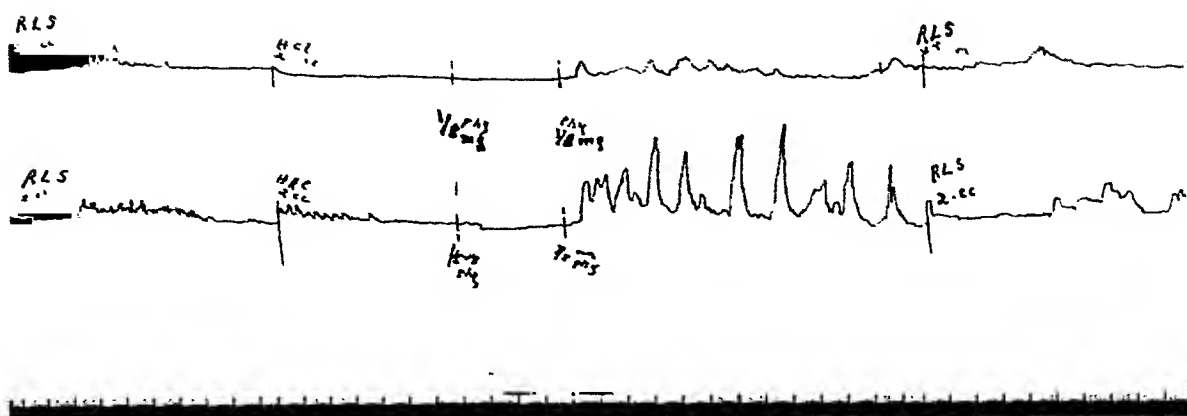


Fig. 2. Cat—wt. 3.4 kgm. Upper tracing—hydrochloric acid 0.00219M. Lower tracing—acetic acid 0.303M. Physostigmine  $\frac{1}{8}$  mgm. (repeated). R. L. S. = Ringer-Locke Solution.

repeated with similar results. A minute or two later the loops were emptied, washed out and rested. Ten minutes afterwards they were filled with Ringer-Locke solution. Physostigmine was then given, with the result that the loop which had held the acetic acid showed strong spasmodic contractions, while the other loop continued in its previous state of activity, exhibiting chiefly a display of pulsating rings. The remainder of the gastro-intestinal tube showed no spasmodic contractions during this experiment.

It was also noted in these experiments that the effect of acetic acid was always more prolonged than that of hydrochloric acid. This might of course be due to the property which .04M hydrochloric acid possesses of producing an inhibitory phase. These experiments, however, are only preliminary and a more thorough investigation should be carried out. We consider them merely as possible evidence that the effect of neural

stimulation through the vagus may combine with that of chemical stimulation produced by certain "natural chemical stimuli."

### DISCUSSION

Since the three acid solutions used in *Series A* had an equal H ion concentration, the difference in motor effect produced by each acid could not have been determined in these experiments by a difference in the H ion concentration in the three solutions.

The difference between the three acids, in effectiveness as motor stimulants might be determined by one, or both, of two factors, *viz.*:—the concentration of the anion and the chemical nature of the anion, in the three solutions.

It was necessary in making the solutions isotonic with blood to add a small amount of sodium chloride, about the same for each, to the solutions of hydro-

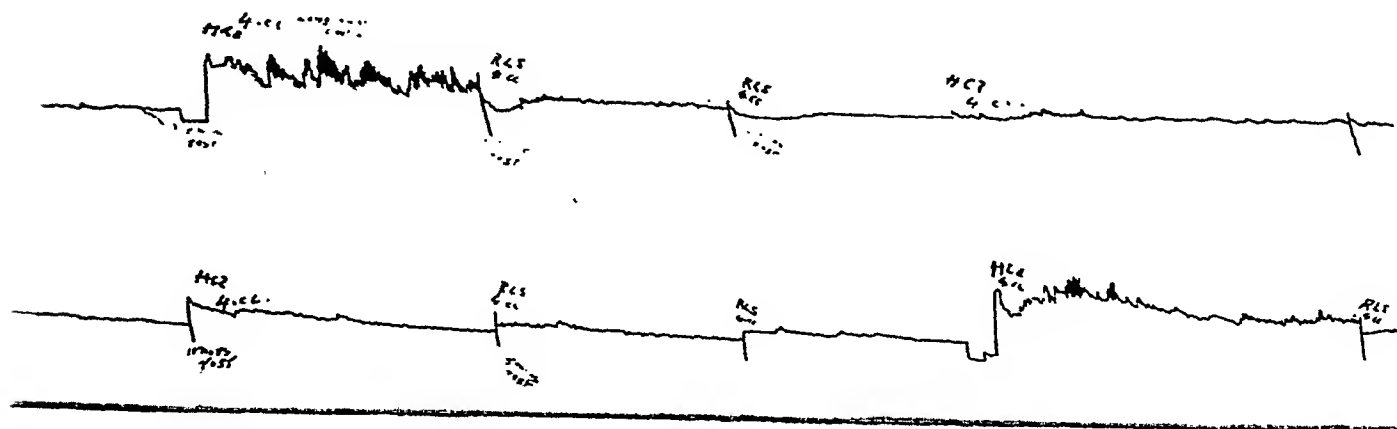


Fig. 3. Cat—wt. 3.1 kgm. Upper tracing—lactic acid 0.04 M; then hydrochloric acid 0.00219M. Lower tracing—hydrochloric acid 0.00219M; then lactic acid 0.04M.

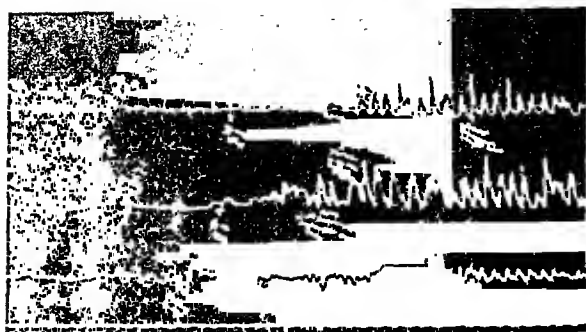


Fig. 4. Cat—wt. 3.4 kgm. Upper tracing—lactic acid 0.04M. Lower tracing—acetic acid 0.303M. Blood pressure tracing. Choline hydrochloride 2.0 mgm. Physostigmine  $\frac{1}{8}$  mgm.

chloric acid and lactic acid. The acetic acid solution at the concentration used was already isotonic with blood and no sodium chloride had to be added.

Thus the solutions of hydrochloric acid and lactic acid each contain the chlorine ion while the acetic acid solution does not. Since the amounts of sodium chloride added to the hydrochloric acid solution and the lactic acid solution were about equal it is obvious that the hydrochloric acid solution will have a much higher concentration of chlorine ions than the lactic acid solution. However, the lactic acid solution was very definitely a better motor excitant than the hydrochloric acid solution. It would seem therefore that the concentration of chlorine ions could not give rise to the results we obtained unless the chlorine ion has an inhibitory effect on intestinal motor activity and of this there is no evidence.

The other anions which played a part in the experiments were the acetate anion and the lactate anion.

Now since the acid solutions which contained these anions had equal concentrations of H ions it follows

that the concentration of these two anions in their respective acid solutions must have been equal and the difference in the effect of the acetic acid and lactic acid solutions could not have been due to a different concentration of their anions.

From the above analysis it does not seem probable that the concentration of the anions in the solutions played a very important role in the results obtained and the latter would appear to have been determined by the chemical nature of the anion.

The above statement is not meant to minimize the importance of other factors, such as the concentration of the ions, for it is realized that if different concentrations are used this chemical effect of the ion might not be apparent.

Babkin (1916) showed the importance of the concentration factor in the response of the gut to hydrochloric acid for example, and in some other experiments of our own with solutions of hydrochloric acid, acetic acid and lactic acid solutions of equal molar concentration (0.04M), equivalent to a titratable acidity of .15% hydrochloric acid, the hydrochloric acid proved to be a much more active stimulant than either of the organic acids. It is interesting to note that in these experiments with acids of equal molar concentration the acetic acid and lactic acid solutions were about equally effective although as a matter of fact the concentration of anions in the lactic acid solution was about four times that in the acetic acid solution.

The physostigmine and choline were employed in the present work in an effort to investigate further the manner in which the acids produced their effects.

In discussing the mechanism of the action of the acids on the motility of the small intestine we are merely putting forward some suggestions, since the experimental material does not permit of any more definite conclusions being drawn. Further work of a

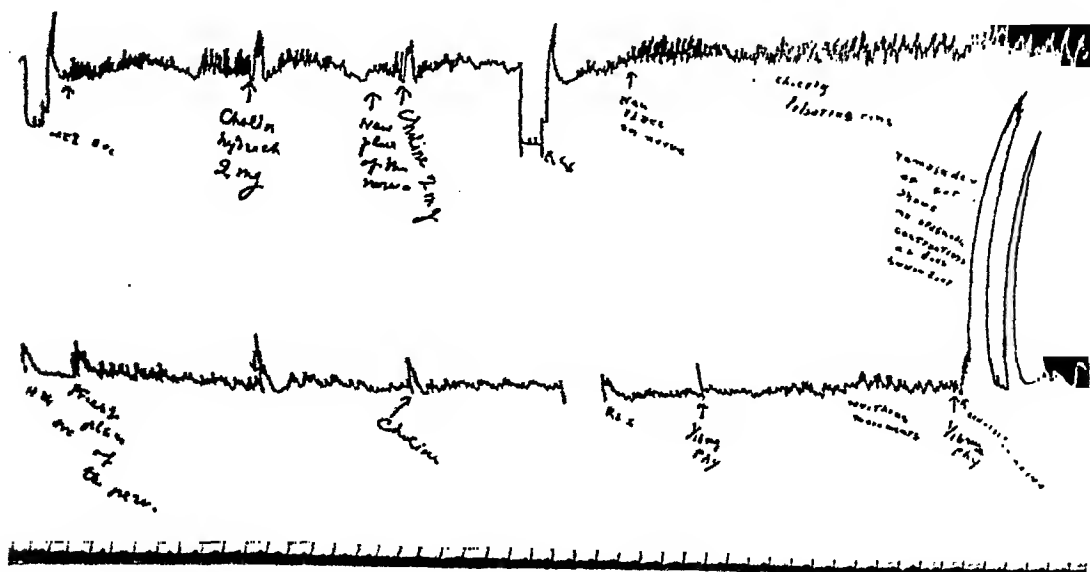


Fig. 5. Cat—wt 3.2 kgm. In duodenal coil at 9 cm., on right: varus. Upper tracing—hydrochloric acid 0.04M. Lower tracing—acetic acid 0.1M. Choline hydrochloride 2.0 mgm. (repeated). Physostigmine  $\frac{1}{16}$  mgm. (repeated).



specialized nature is needed in order the more fully to elucidate this important problem.

One explanation of the stronger effect of the acetic acid as compared with hydrochloric and lactic acid may be based on the physico-chemical properties of the organic and inorganic acids. Organic and inorganic acids, although having the same pH, penetrate through the cell membrane with different velocities, which may be due to the greater solubility of the organic acids in lipoids. In our experiments this fact may have determined the greater effect of the organic acids than of hydrochloric acid upon the neuromuscular apparatus of the gut.

Another explanation, however, may be given, based on the modern conception of "local hormones" or the "chemical transmission of nerve impulses." As histological study of the distribution of the capillary blood vessel net and of the lymph vessels shows, it is quite possible that a solution absorbed from the intestine before it enters the general circulation may act on the nerves and muscle elements of the gut. Therefore, the acid solutions which we used in our experiments could have affected the neuro-muscular apparatus of the intestine and those chemical bodies, such as choline, which are considered necessary for originating the spontaneous motility of the alimentary canal as well as for transmitting the impulses from the pre-ganglionic to the post-ganglionic autonomic nerves.

In the light of recent investigations the earlier observations on the stimulating effect of salts of various fatty acids on isolated strips of small intestine become of increased interest. Rona and Neukirk (1912) showed that the salts of acetic and pyruvic acid were especially stimulant. LeHeux (1921) studied the effects of a series of sodium salts of formic, acetic, propionic and other acids and the effects of the corresponding esters of these acids formed with choline. There was a striking parallelism in the effects of the two series, and the effects of both were inhibited by atropine. He observed that washing of the gut strips inhibited the characteristic effects of the salts but that the addition of choline restored the activity of the strips. He concluded that probably there is present in the gut some enzyme capable of synthesizing choline and acids to form the ester, and that the stimulating activity of the acid depends on this reaction. Further work by Abderhalden and Paffrath (1925), Loewi and Navratil (1920) and Plattner and Hinter (1930) gives strong support to the idea of the presence of such an enzyme in the gut.

In connection with the above theory we believe that the following facts brought out by our work are of some significance:

(1) That physostigmine and choline greatly increased the effect of acetic acid in comparison with that of hydrochloric acid and lactic acid.

(2) That very often under the combined action of acetic acid and physostigmine spasmodic contractions were noted; this type of contraction may be regarded as representing the strongest activity of the gut.

To conclude, it must be emphasized once more that we merely suggest some explanations, fully realizing that the true mechanism of the action of acids on the intestine can only be disclosed by further investigation. However, even the facts reported in the present study, as well as the work of our predecessors, clearly indicate how important is the part which various natural chemical stimuli play in maintaining the normal motor activity of the gastro-intestinal tract.

It seems highly desirable to extend these studies in order that it may be possible to deal in a more rational way with many motor ailments of the gastro-intestinal tract.

### SUMMARY

The effect upon intestinal motility of isotonic solutions of hydrochloric acid, acetic acid or lactic acid, introduced into the lumen of the small intestine of the cat, was investigated. The action, upon the response provoked by the acid solutions, of subminimal doses of physostigmine and choline hydrochloride given intravenously was noted.

Two series of experiments were performed:

#### SERIES A

In this series the three acid solutions were of equal pH. It was found that:

(1) The acetic acid solution was the most effective motor stimulant.

(2) The lactic acid solution was more effective than the hydrochloric acid solution.

(3) Physostigmine and choline accentuated the above-noted differences in the motor response to the three acid solutions.

#### SERIES B

In this series only hydrochloric acid and acetic acid were used. The hydrochloric acid solution was more concentrated and the acetic acid solution less concentrated than in Series A. Rhythmic vagal stimulation was employed in each experiment. It was found that:

(1) The acetic acid solution was not much more effective as a motor stimulant than the hydrochloric acid solution.

(2) Physostigmine and choline enhanced the effect of the acetic acid solution more than it did that of the hydrochloric acid solution.

The Author wishes to thank Dr. B. P. Babkin for suggesting this problem and for his helpful advice and criticism during the progress of the work.

### REFERENCES

- Abderhalden and Paffrath: *Fermentforsch.*, 8:299, 1925.  
 Babkin, B. P.: *Bull. de l'Acad. Imp. des Sci. de Russie*, p. 999, 1916.  
 Babkin, B. P.: *Quart. Jour. Exper. Physiol.*, 14:259, 1924.  
 Babkin, B. P.: *Can. Med. Assoc. Jour.*, 15:719, 1926.  
 Babkin, B. P.: *Can. Med. Assoc. Jour.*, 18:267, 1928 (a).  
 Babkin, B. P.: *Die äussere Sekretion der Verdauungsdrüsen*, p. 842. 2nd ed. Berlin, 1928 (b).

- Le Heux: *Pflügers Archiv*, 190:280, 1921.  
 Loewi and Navratil: *Pflügers Archiv*, 214:678, 1926.  
 Magnus: *Münch. med. Wochenschr.*, No. 7:249, 1925.  
 Plattner and Hinter: *Pflügers Archiv*, 225:19, 1930.  
 Rona and Neukirk: *Pflügers Archiv*, 146:371, 1912; 148:273, 1912.  
 Thomas, J. S., and Morgan, C. J.: *Proc. Soc. Exp. Biol. and Med.*, 28:968, 1931.

## SECTION III—Nutrition

### Blood Buffer Values in Mineral Deficiency\*

By

I. NEWTON KUGELMASS, M.D.

NEW YORK, NEW YORK

THAT rachitic infants have a relatively unstable acid-base mechanism has been a consistent clinical observation when compared with well nourished infants. To be sure, it is a consequence of infectious invasion but the extent of the disturbance is much too striking to be passed up as a concomitant of the rachitic state. The acid-base disturbance either manifests itself as an alkalosis of some form with or without latent or active tetany. These deviations from biologic neutrality are exceptional in the normal child thus indicating the relative buffer stability of all its tissues.

Furthermore it has been observed, in experimental studies with rachitic animals, that it takes less acid or alkali to disturb the acid-base equilibrium of the rachitic than it does of normal animals. Some workers have attempted to explain these differences in acid-base behavior by seeking for a non-existent lowered alkali reserve or a negligible diminution in blood pH. We have, therefore, approached the problem by determining the buffer capacity of the blood of rachitic infants in comparison with that of normal infants as a biochemical refinement for the interpretation of the acid-base behavior in the rachitic state. This study is an application of the physical chemistry of the buffer mechanisms in heterogeneous systems as developed by the Author (1) in 1924.

Buffer capacity of a solution represents the known equivalents of either acid or alkali necessary to be added to the solution or lost from it in order to alter it by one unit of pH. Clinically the buffer capacity of blood is more frequently altered by a loss of bases in diarrhea and acids in vomiting than by frank addition of either acid or base for therapy. The buffer capacity of such an ideal buffer system, as blood, constitutes therefore its degree of stabilization to alteration in that narrow range of acid-base equilibrium which is most favorable for normal life function. This buffer capacity is additive in that it constitutes the buffer values of the individual buffer systems which are contained in blood—the proteins, phosphates, carbonates, etc. Any depletion in any one of these blood components in disease necessarily diminishes the total buffer capacity of the blood although it may not become manifest as a change in pH or in vol. of  $\text{CO}_2$ . Buffer value is further differentiated from potential acidity

which is the amount of alkali necessary to neutralize the available acidity in a definite amount of solution.

The buffer value, B, of serum at a given pH may be determined practically by electrometric titration. Strong standard acid or alkali is added to the serum in increasing amounts and the pH determined after each addition. If the concentration of added acid or alkali be great enough to keep the maximum increase in volume of the buffer solution relatively small, the volume may be neglected as the pH changes of buffer solutions are but slightly affected by volume changes of such magnitudes. Addition of each cubic centimeter of 0.1N. NaOH to serum of original volume 5 c.c. produces an increase of  $\Delta B = \frac{1}{V}$ . The buffer value  $\frac{\Delta B}{\Delta \text{pH}}$  at any pH may be determined graphically by plotting on a coordination system pH as ordinates, equivalents of alkali to the right and equivalents of acid to the left, as abscissae. The buffer value is the slope of the line tangent to the curve at the pH required.

#### PROCEDURE

The hydrogen ion concentration of the alkaline titrations was determined electrometrically by a Leeds and Northrup direct reading potentiometer of low resistance with enclosed lamp and scale galvanometer; a Weston standard cell; saturated KCl calomel and hydrogen cells and platinized platinum electrodes. The measurements were standardized by 0.05N, KH phthalate solution. The hydrogen ion concentrations of the acid titrations were determined by the quinhydrone electrode consisting of a bright platinum wire immersed in a solution containing quinhydrone to the extent of about 0.005N. This is the simplest of electrodes, the potential established being a linear function of the hydrogen ion concentration up to pH 8. Foaming of the solution in the alkali range was prevented by drops of amyl alcohol.

Five cubic centimeters of serum from normal and rachitic infants respectively were introduced into the titration chamber, the pH determined electrometrically at equilibrium and the acid titration carried out by the addition of successively increasing amount of 0.1N, NaOH and the resulting pH similarly measured in each case. The pH values were plotted against the total concentration of standard acid and alkali added. These titrations included a wide pH range with a total volume maintained in each case of about 10 c.c. or about twice the initial serum content. This represents

\*From the Heckerling Institute, New York City.  
Submitted July 12, 1935.

the optimum limit for utilizing buffer values with some degree of accuracy because dilution necessarily decreases buffer capacity. The purpose of the problem is the comparative evaluation of normal and rachitic serum rather than absolute determination of their buffer values.

### RESULTS

Three striking buffer curves are obtained from these electrometric titrations of the relative buffer

capacities of serum of normal and rachitic infants in comparison with that of physiologic saline. The buffer value of a non-buffer system upon additions of strong acid or alkali is slight within the pH range biologically significant. If there were no buffering at all, each addition of acid or alkali would produce infinite change in pH. The graph (Fig. 1) shows that the buffer value of completely dissociated acid or alkali is slight indeed, too slight in fact to be evident on the scale represented.

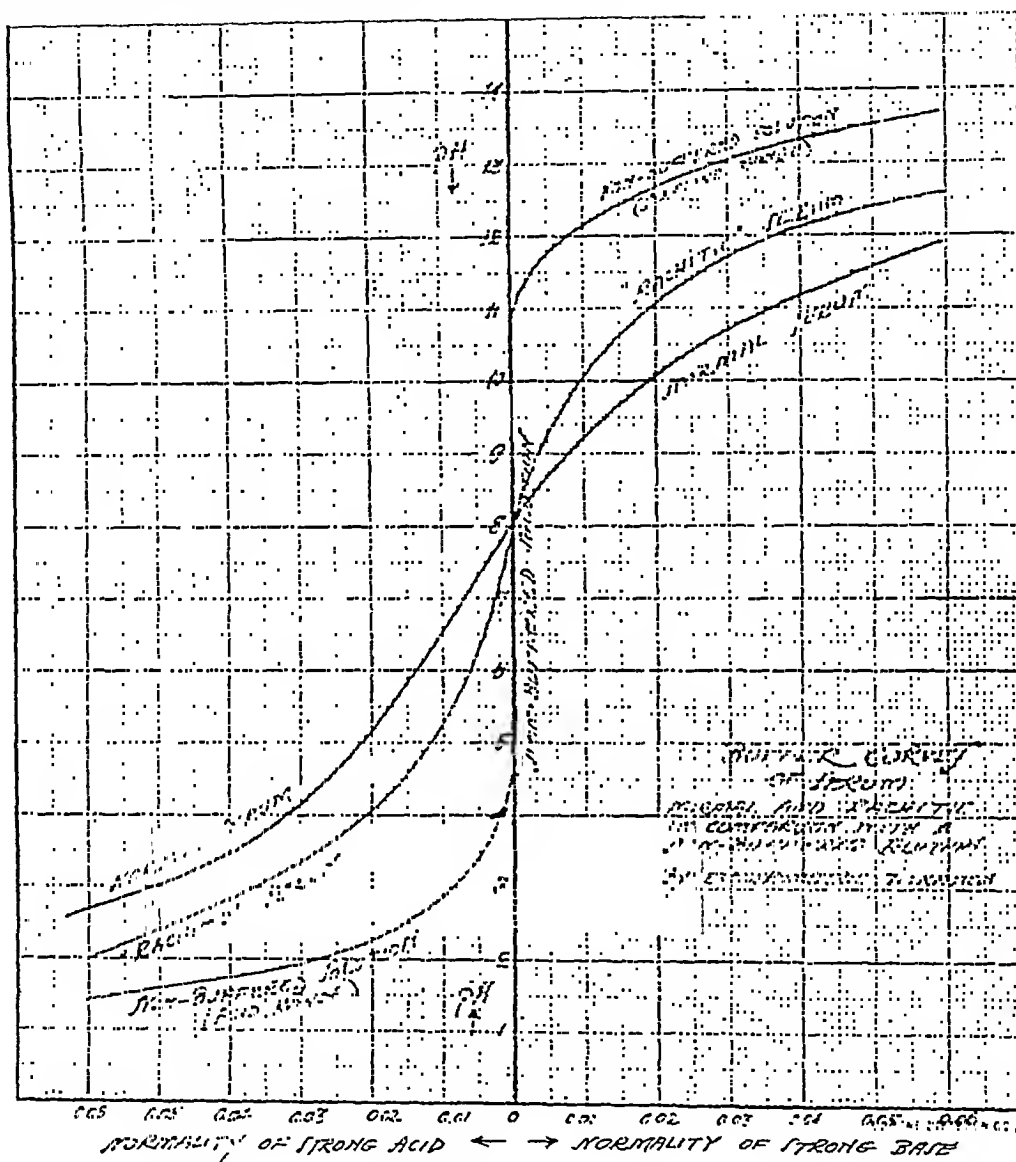


Figure 1

Electrometric Titration Values of Serum

| Titer     | Equiv. | Normal Serum |       | "Rachitic" Serum |       |       | Saline |
|-----------|--------|--------------|-------|------------------|-------|-------|--------|
|           |        | I            | II    | I                | II    | III   |        |
| N/10 NaOH |        |              |       |                  |       |       |        |
| 0.5       | .005   | 8.05         | 8.12  | 8.10             | 8.35  | 8.30  | 6.6    |
| 1.0       | .010   | 8.72         | 8.60  | 9.30             | 9.42  | 9.40  | 11.8   |
| 2.0       | .020   | 9.20         | 9.32  | 10.10            | 10.25 | 10.22 | 12.4   |
| 2.8       | .028   | 10.10        | 9.85  | 11.00            | 10.90 | 11.10 | 13.0   |
| 4.2       | .042   | 10.50        | 10.55 | 11.50            | 11.60 | 11.65 | 13.0   |
| 6.0       | .060   | 11.20        | 11.28 | 12.00            | 11.95 | 11.95 | 13.4   |
|           |        | 11.90        | 12.02 | 12.50            | 12.55 |       | 13.5   |
| N/10 HCl  |        |              |       |                  |       |       |        |
| 0.7       | .007   | 7.20         | 7.45  | 6.50             | 6.65  | 6.62  | 2.8    |
| 1.0       | .010   | 6.35         | 6.20  | 5.60             | 5.62  | 5.70  | 2.6    |
| 1.5       | .018   | 5.30         | 5.25  | 4.45             | 4.50  | 4.52  | 2.5    |
| 3.0       | .030   | 4.00         | 4.10  | 3.62             | 3.65  | 3.70  | 2.2    |
| 4.0       | .040   | 3.52         | 3.40  | 2.80             | 2.95  | 2.92  | 2.0    |
| 6.5       | .065   | 2.55         | 2.70  | 2.12             | 2.25  | 2.28  | 1.6    |

But at both ends of the graph of this non-buffered solution the buffer value becomes quite significant. This stoichiometric behaviour between pH 3 and 11, representing the neutralization of acid and base, and the alkaline buffer effect beyond pH 11 and the acid buffer effects below pH 3, are demonstrable both chemically and mathematically. Further physico-chemical discussion is beyond the purpose of this paper. Its graphic inclusion has only been made for control comparison of the buffer behaviour of the sera of normal and rachitic infants.

The buffer value of normal serum on both acid and alkali sides of the pH axis shows a sloping more and more marked as one recedes from neutrality in both extremes. The degree of sloping at any pH represents the total buffer capacity of the serum at that pH. The contrast between the curve of the non-buffered solution which falls over the pH axis between 3 and 11 and that of normal serum is quite marked. Although blood is an unusually ideal buffer system it is not constant in its buffer action but rather varies with each pH region. In fact, it appears most strongly buffered on the acid side below about pH 5, that is, below the iso-electric points of serum albumin and globulin when in this acid region they begin to act as electro-positive chemical constituents. The mechanism of this interesting behaviour is beyond the purpose of the present paper. Another interesting observation deduced from the buffer curve of normal serum is that its buffer value in the alkali range is greater than that on the acid range. This explains, for example, why frank acidosis is much more prevalent than is alkalosis. It also reveals the protective mechanism available in the blood in the prevention of alkalosis, inasmuch as the pH range on the alkaline side compatible with life is much more limited than that on the acid side.

The buffer curve of the sera obtained from rachitic infants is very definitely between the normal buffer curve and the control curve of a non-buffered solution. The striking diminution in buffer capacity of rachitic serum offers a substantial basis for the instability of the acid-base mechanism in rachitic infants. This diminution in buffer capacity is evident on both acid and alkaline sides thus making the development of both acidosis and alkalosis a more prevalent concomi-

tant of rickets when precipitated by acute infectious disease. The relative course of the buffer curve in rickets is not unlike that of the normal curve except for the fact that the area lying between the rachitic curve and the non-buffered curve represents a buffer capacity considerably diminished in comparison with the larger area occupied by the normal buffer curve.

The *therapeutic consequence* that follows from these observations on the diminished buffer capacity in rickets is for the administration in the dietary of the base-forming foods, as milk, fruits, and vegetables in addition to the anti-rachitic specific, vitamin D. There has been so much emphasis placed on the vitamin side of rachitic therapy that the intrinsic mechanism of the healing has been more or less lost sight of in routine clinical procedure. Vitamin D specifically catalyzes the absorption and utilization of calcium and phosphate salts but can do no more as far as the rachitic processes are concerned. Without calcium and phosphate salts made available in the dietary, vitamin D alone cannot induce calcification. In addition to the body depletion in bone constituents, the other buffer salts are evidently likewise decreased in content and must be made up in the daily dietary by sufficient addition of base-forming salts (2).

### CONCLUSIONS

1. The buffer values of serum obtained from normal and rachitic infants have been determined electrometrically for the entire pH range.
2. The blood buffer curves of normal and rachitic infants plotted against that of a non-buffered solution show the marked diminution in the blood buffer capacity in rickets.
3. The buffer action of blood is not constant but is determined by the pH at which it reacts.
4. The buffer capacity of normal serum is greater on the alkaline side than it is on the acid side within the biological range of pH 5 to 8.5, beyond which the buffer values of serum become markedly accentuated.
5. The diminished buffer capacity of the serum of rachitic infants at all pH ranges explains the relative instability of the acid-base mechanism in rickets.

### REFERENCES

1. Kugelmann, I. N.: *J. Biol. Chem.*, 60, 227, 1924.
2. Kugelmann, I. N.: *Am. J. Dis. Children*, 39, 687, 1930.

## Statement

In the October issue of this Journal appeared an article by the undersigned called "A Year's Exclusive Meat Diet and Seven Years Later," in which was reported the present health status of Mr. Vilhjalmur Stefansson, the subject of the article.

Mr. Carson Anderson, who with Stefansson subsisted on an exclusive meat diet for one year and whose case was intensively studied at the Russell Sage Foundation, has just finished a health audit in my office. It will be recalled that Mr. Anderson spent four years with Mr. Stefansson in the Arctic circle.

Mr. Anderson has been in excellent health since the experiment. He is now forty-five years of age and weighs one hundred seventy-four pounds. He looks in fine physical trim and has no neurocirculatory, gastro-

intestinal or genito-urinary symptoms. His hair, though never thick, is in the same condition it was six years ago. The teeth and gums have shown no striking change over what was found during hospitalization six years ago. His blood pressure is 135/85. Blood and urine normal in every particular. All special senses are unimpaired, vision is perfect without the use of glasses. Mr. Anderson's diet has consisted largely of bread and potatoes with more meat than the average person eats. He takes a small amount of fruit and green vegetables daily and not more than one glass of milk per week and very little butter and cream.

Clarence W. Lieb, A.M., M.D.,  
New York, New York.

## SECTION V—*Therapeutics*

### A New Technique for the Continuous Control of Acidity in Peptic Ulcer by the Aluminum Hydroxide Drip

By

E. E. WOLDMAN, M.D.

and

V. C. ROWLAND, M.D.

CLEVELAND, OHIO

**D**URING the last five years, considerable experimental and clinical evidence has accumulated to indicate that the acid factor is really important as an immediate or exciting cause of peptic ulcer and of its persistence in chronic form. There is no doubt about the profound significance of a number of predisposing causes of clinical ulcer—the neurogenic, vascular, traumatic, infectious, toxic and possibly hormonal or other X factors. These predisposing conditions in different degrees in individual cases render the local tissues vulnerable to the attack of the acid gastric juice. The length of time the tissues are exposed to this action is also important. Nervous disturbances and spasm of the pylorus interfere with the normal regurgitating and neutralizing mechanism which seems to provide an important protection to the ulcer bearing area.

Mann's "Surgical Duodenal Drainage" operation which diverts the alkaline juices to the lower intestine and attaches the jejunum directly to the pylorus leads almost uniformly to ulceration just beyond the pylorus. That the acid factor is the important one from the experimental standpoint is well confirmed by the work of Elman and Hartman, Morton, Mathews and Dragstedt, Weiss and Hubster and other well known investigators in this field.

Clinically, there is evidence that a similar mechanism exists, however much it may be modified by other factors. It is suggestive to find peptic ulcer occasionally adjacent to a Meckel's diverticulum or wherever there is aberrant gastric mucosa. This has been demonstrated at the umbilicus with the secretion of free hydrochloric acid and pepsin and ulceration of the surrounding skin. (Aschner and Karelitz: *Ann. of Surg.*, 91:573, 1930). Thirty-three cases of chronic ulcer with pain, hemorrhage or perforation and characteristic histology of peptic ulcer have been described in the neck of a Meckel's diverticulum in the adjacent ileum.

As a final evidence of the importance of the acid factor in the etiology of human peptic ulcer, the following personal experience with duodenal suction siphonage may be cited.

A well nourished woman of 33 years with an essentially negative past history was admitted to the hospital with jaundice and a complaint of three weeks of gall bladder pain. She grew sicker and pain shifted to the left hypochondrium with slight rigidity. The temperature was 37.5 to 38.5. White blood count was 18,000, icteric index 16, urine showed sugar and blood sugar was 153. A diagnosis of pancreatitis was made and the suction siphonage regimen instituted. It was continued with short interruptions for over three weeks. The details of her course are irrelevant here, but the patient finally died of infectious complications, about five weeks after hospitalization.

Autopsy confirmed the pancreatitis and complications but the finding of special significance in connection with the prolonged aspiration of duodenal contents was the presence of three large acute duodenal ulcers histologically typical of acute peptic ulcer.

This case seems really to present a clinical duplication of the above experimental conditions. It indicates that in human beings as in dogs the prolonged action of acid gastric juice unneutralized by the duodenal contents may lead to ulcer. If this is true, the logical first step in treatment and the most direct attack upon the lesion is the continuous neutralization of the acid. At the same time physical and mental rest, appropriate diet and medication may be used.

The great difficulty of medical ant-acid treatment aside from the menace of alkalosis has been its intermittency especially its discontinuance during the long night period. By the continuous instillation of an adsorbent substance with the indwelling nasal Levin tube night and day a constant control may be attained and readily checked at any time by aspirating samples. Soluble alkali in milk as used by Winkelstein has several disadvantages. Aluminum hydroxide is an amphoteric adsorbent substance which is not absorbed from the gastro-intestinal tract in any appreciable amount. Victor Myers by blood analysis found from five to twelve hundredths of a milligram of aluminum to one hundred cubic centimeters of blood after the ingestion of 168 cubic centimeters of a heavy suspension of precipitated aluminum hydroxide. Such minute traces are sometimes found normally without medication. No irritation of the gastro-intestinal or urinary tract is observed and the CO<sub>2</sub> combining power of the blood and Ph remain unchanged. Six hundred cubic

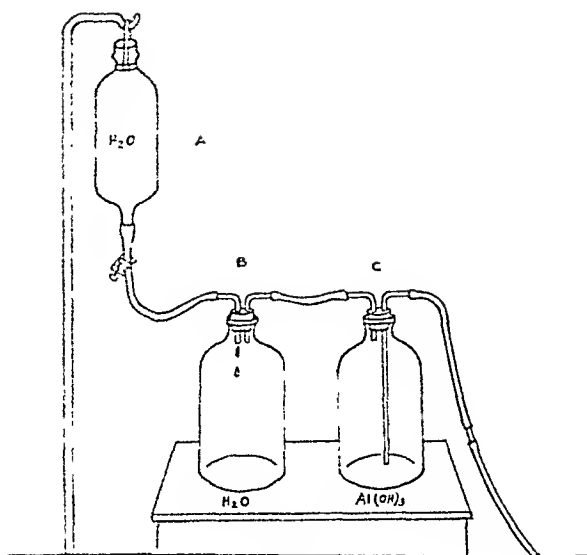


Fig. 1

centimeters of the concentrated suspension of aluminum hydroxide precipitate were used daily and apparently any reasonable amount may be used with impunity.

A seven per cent colloidal suspension of aluminum hydroxide will adsorb twenty times its volume of N 10 hydrochloric acid. A fresh, washed, flocculent

precipitate of the hydroxide made from a solution of aluminum chloride is very efficacious, but the dry powder or tablets break down to oxides or other inert substances which by direct titration have little or no effect as an ant-acid. Colloidal milling of the washed precipitate greatly enhances the adsorbent properties, apparently by increased surface tension. It requires as long as 40 minutes for the colloidal jelly to exert its complete ant-acid effect. By this method, symptomatic relief is usually prompt and X-ray evidence is at hand to show that an extraordinarily rapid rate of healing of sizeable deformities of the lesser curvature may be attained.

The seven per cent suspension is too gelatinous to flow freely through a constricted tube and is also much more concentrated than necessary for the continuous drip. Furthermore in a simple drip arrangement with a Levin tube there is an accumulation of fluid in the dependent part of the tube with an intermittent discharge into the stomach of a large quantity followed by a period with no flow.

#### THE APPARATUS

The apparatus (Fig. 1) consists of an elevated bottle of water with a tube outlet and a simple clamp allowing water to drip into a lower bottle, which in turn is attached to a siphon system filled with a large supply of diluted (about 1%) aluminum hydroxide suspension. The filled siphon system, the outflow of which is a Levin tube may be tested before hand. It is readily seen that the water drip inflow releases the

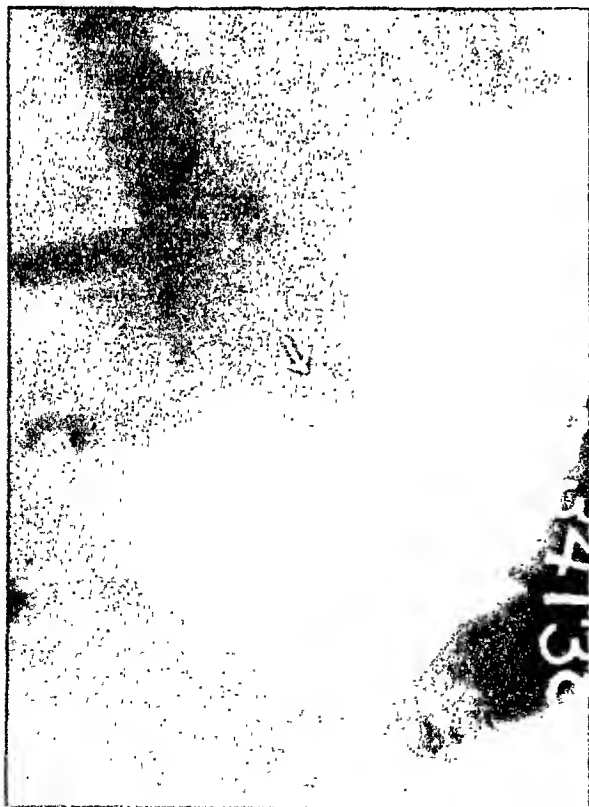


Fig. 2

Case 1. L. S., 34 years, male, laborer. A. Gastric ulcer on the lesser curvature at the beginning of treatment. (4 plates). Also typical fluoroscopically. B. Seven days later: Ulcer deformity entirely gone. (Four other plates of the stomach taken at this time, at all angles, showed no deformity).



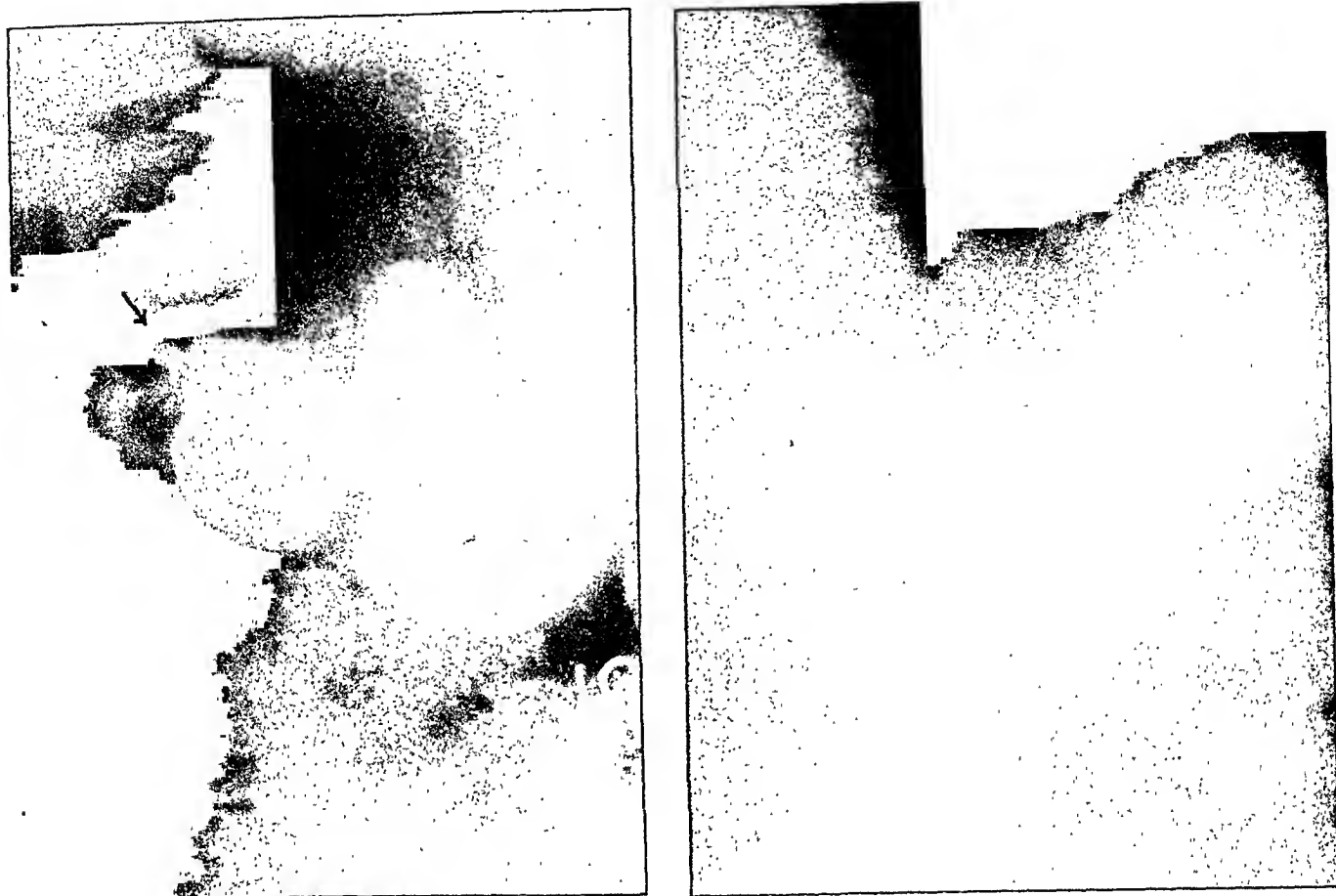


Fig. 3

Case 3. C. J. S., 38 years, male, school teacher. A. Ulcer at the outlet of the stomach or first part of the duodenum at the beginning of treatment. (3 plates). B. Seven days later: The crater of the ulcer is no longer demonstrable. (Four other plates taken at this time, at all angles, did not show the crater of the ulcer).

siphon system outflow at precisely the same rate, that is drop by drop. When the Levin nasal tube is in the patient's stomach, the outlet being at a somewhat lower level than the supply bottle, there is a continuous drip of the aluminum hydroxide suspension fully controlled by the water drip. The system is automatic, simply requiring to be kept air tight and replenished with water and aluminum hydroxide suspension each morning.

#### METHOD OF PROCEDURE

A small Levin tube, size 12, is passed through the patient's nostril into his stomach. A specimen of gastric content is withdrawn for analysis and also to show that the tip of the tube is in the stomach. About 200 c.c. of 7% colloidal aluminum hydroxide is added to 600 c.c. of distilled water and stirred until well mixed. The 800 c.c. of the diluted aluminum hydroxide is poured into bottle (C). The gravity flask (A) is filled with water while the clamp is closed. Allow the aluminum hydroxide to siphon from bottle (C) into a pan until it ceases. At this time there is a negative pressure created in bottle (B) and above the fluid level in bottle (C). Now connect the tube to the Levin tube and adjust the clamp beneath flask (A) so that the water will drip from flask (A) into bottle (B) at the rate of 5 or 6 drops per minute. Each drop creates that much positive pressure in bottle (B) and causes a drop to drip from the end of the Levin tube into the stomach. As the fluid level rises in bottle (B) it will cause the fluid level to fall proportionately

in bottle (C) and at the rate of 5 or 6 drops per minute it will take 24 hours to be completely empty. The entire system must be air tight.

#### RESULTS

In a small group of cases, prompt relief from pain especially night pain was one of the striking results. A constant achlorhydria was produced as proved by frequent sampling during the day and before the morning feeding. One recent case had persistent pain after four weeks in bed on a Sippy routine and was referred for surgery. This case was pain-free within one week on the above treatment. There is very little discomfort with the nasal tube, warmed before insertion, lubricated if necessary with plain mineral oil and attached with adhesive to the face. Cases with definite X-ray deformities were selected and a number of films in several directions taken at the end of one week. The rapidity of change was very striking. Gastric ulcer of course lends itself better to the demonstration of the structural change. Duodenal ulcer may heal and leave a deformed cap, but in the case below a definite ulcer crater later disappeared in one week's time. Dr. R. J. May, roentgenologist of St. Luke's Hospital made a special effort to demonstrate these lesions after the special treatment (Figs. 2, 3).

#### SUMMARY

We believe this method of continuous twenty-four hour adsorption of gastric acidity by aluminum hydro-

xide has promise of definite usefulness in the treatment of the acute stage of peptic ulcer. If reliance is placed on ant-acid treatment, there is every reason to carry it out in the most thorough and continuous manner. The aluminum hydroxide drip is free from the danger of alkalosis and of secondary acid secretion. The method is entirely compatible with any type of dietetic or sedative treatment. Because of continuous

neutralization the diet can be suited more definitely to the nutritional needs of the patient rather than crowded in frequent feedings to control acidity. Functional rest of both the secretory and motor function of the stomach may be allowed in larger measure. Especially for the intractable case, before surgery is resorted to, this method represents an additional refinement of technique in medical management.

#### REFERENCES

1. Mann and Williamson: The Experimental Production of Peptic Ulcer. *Ann. Surg.*, 77:109, April, 1923.
2. Mathews: Production of Intestinal Ulcers by Active Gastric Juice. *Proc. Soc. Exp. Biol. and Med.*, 28:960, June, 1931.
3. Mathews and Dragstedt: The Etiology of Gastric and Duodenal Ulcer. *S., G., and O.*, 55:265, September, 1932.
4. Elmar and Hartman: Spontaneous Peptic Ulcers of Duodenum After Continued Loss of Total Pancreatic Juice. *Arch. of Surg.*, 23:1030, December, 1931.
5. Einsel and Rowland: The Aluminum Hydroxide Treatment of Peptic Ulcer. *Ohio State Med. Jour.*, March, 1932.
6. Mann and Bollman: A Symposium Concerned with the Duodenal Factors in the Neutralization of Acid Chyme. *Amer. Jour. Digest. Dis. and Nutr.*, Vol. 11, pp. 284-305, July, 1935.

## Therapy of Peptic Ulcer: Conservative Versus Radical\*

By

ERNEST H. GAITHER, M.D.  
BALTIMORE, MARYLAND

IN all fields of endeavor in which worthwhile progress has been achieved, frequent, earnest and at times acrimonious controversial arguments have been rife. Medicine is no exception to the rule; and during the past few years, the proponents and opponents of various types of therapy relating to peptic ulcer have been extremely active in publishing views extolling or decrying this or that new remedy, and defending or attacking what may be termed the "older" types of therapy. The opportunity for comparison afforded by bringing together for calm consideration sharply differing views, cannot but be conducive to continued progress.

Of late years, myriads of new therapeutic agencies for the treatment of peptic ulcer have been brought forward; many of these are parenteral methods; each remedy has been presented by some author as the only true *sine qua non* for the alleviation or cure of peptic ulcer. To present only a part of this array, one may mention the following remedies: Non-specific proteins, aolan, histidine, mucin, vitamin-C; diathermy of the cervical, sympathetic and parasympathetic ganglia by short waves; local application of radioactive substances; colloid aluminum hydroxide; injectable extract of pituitary lobe; specific vaccine; injections of parathyroid extract; amino-acids; insulin; intravenous injections of sodium benzoate. Various theories as to why these remedies should prove efficacious have been advanced.

Martin thinks it likely that ulcer in man may be the result of a reaction of sensitized cells to a specific antigen; the ulcer is simply an allergic phenomenon, and the aid brought about by the parenteral injection of milk protein may be due to a non-specific desensitization of the sensitized cells. He cites German authorities who are of the opinion that the intravenous injection of a foreign protein brings about a "shock" and the results are due to the ensuing reaction.

Martin's results in 95 patients observed over a period of 4½ years are as follows: 78 per cent had been greatly improved or clinically cured; a greater percentage of those whose symptoms had existed for only a few months were clinically cured or improved, that is, 86.4 per cent. One to four years after treatment, 60 per cent of the 60 cases who reported were clinically cured or improved. Of those whose symptoms had existed less than one year prior to treatment, 77.9 per cent were improved or clinically cured.

It is to be noted that Martin invariably states that the patients were "clinically cured or improved," and fails to state that the percentages given are indicative of unqualified healing and a complete relief of the condition. In this connection it is interesting to quote him as to the roentgen-ray proof of healing. He states: "Films taken from 2 to 18 months after the end of treatment frequently did, however, show definitely less spasm. Occasionally a smaller defect was seen; but in most cases no change was noted."

Schiff states that protein therapy results in either increased antibody formation or increased mobilization of pre-formed antibodies, and, further, that increase in agglutinins has been demonstrated to follow injection of albumose and nuclein, and milk protein. Protein injections may also act as non-specific desensitizing agents; and there is increasing evidence that the process of desensitization is not strictly specific. His investigations were made on a series comprising 27 cases of duodenal ulcer, the patients being given 10 c.c. of "aolan" intragluteally twice weekly for an average of 10 injections; 20 of the cases were allowed to continue their work and no diet or drugs were prescribed. Marked improvement or practically complete symptomatic relief occurred in 18, or 66.7 per cent; and less marked though definite improvement in 5, or 18.5 per cent, making a total of 85.2 per cent deriving benefit. No constant change in the degree of acidity or volume of gastric juice was noted. Comparative X-ray studies showed that the deformity persisted in all the cases in the series.

\*From the Digestive Clinic of Johns Hopkins Hospital, Baltimore, Maryland.  
Submitted October 25, 1935.

Eads presents a preliminary report after carefully studying a series of 35 cases of peptic ulcer, of which 30 were duodenal and 5 gastric in type. In most instances no special diet or medication was followed. This author made use of "histidine," a 4 per cent solution of the hydrochloride being used; it was given in daily injections of 5 c.c., the intramuscular route being preferred. The best results were obtained when the average course of treatment extended over a 21 to 24 day period. At the outset, he remarks that although orthodox medical and surgical treatment both fail at times to achieve the desired result, the final analysis of cures effected compares favorably thus far with the newer modes of therapy, and only a few of the latter have had sufficiently long periods of observation for any accurate estimation of their real value. He believes that the actual mechanism of the action of this amino-acid in the healing of these ulcers is by no means clear, and comments on the fact that the number of cases observed by him is not large, but compares favorably with the series reported recently by other authors. Bulmer reports on 52 cases, Borgendorfer on 30 cases, Hessel on 22, Weiss, Aron and Lenormand on several small series, Volini and McLaughlin on a series of 21 patients. The reports are for the most part concerned with immediate results, the follow-up of the cases being quite insufficient. However, for the most part, these authors report favorably on the histidine method, and assert that gastric ulcer responded better than duodenal ulcer, as a rule. Bulmer reported 58 per cent symptomatic cures with disappearance of abnormal X-ray findings, 19 per cent clinical improvement with no radiological changes, and 23 per cent failures in his series, of which a large number were gastric ulcers.

Various notations as to changes brought about by this treatment are presented by Eads, but I shall be able to give only a few of these: the acid gastric curve remained generally unaffected except in 5 cases; the improvement symptomatically consisted in relief of discomfort, a gain in appetite and weight, and a tolerance for a more normal dietary; the improvement usually appeared after the fifth treatment. Those presenting an obstructive lesion showed no response to treatment. The X-ray findings were variable: six showed disappearance, eight an improvement, and the remaining 21 no change. Eads' immediate results were as follows: 6 cases (17.1 per cent), showed clinical and X-ray evidence of immediate healing; 8 cases (22.8 per cent), showed evidence of clinical and X-ray improvement; 9 cases (25.7 per cent), showed amelioration of symptoms but no X-ray change; 12 cases (34.3 per cent), were unimproved at the completion of the course of treatment. He expressed the opinion that these immediate results are not so favorable as other authors have reported.

Engel presents the results of his treatment of a group of 70 cases by protein therapy of gastric ulcer in which an ulcer had been demonstrated by roentgenoscopy, gastroscopy or clinical examination. The injections were made intravenously at intervals of 3 to 4 days, from 4 to 12 injections being given. Complete cure was effected in 19 per cent of the cases; great improvement, this is, complete freedom from symptoms, was observed in an additional 39 per cent of the cases; slight improvement was noted in 30 per cent, and in only 12 per cent was the protein therapy

a complete failure. This author considers that these results compare favorably with those of other therapeutic methods, and that ulcers which do not yield to dietetic treatment should be subjected to protein therapy before surgical treatment is applied.

Smithies writes in regard to parenteral therapy: "General impression: helpful, even if not curative, in uncomplicated cases, in approximately 70 per cent; rather a dangerous procedure to place in the hands of general practitioners who may not select cases, or recognize the presence of complications. In addition to the parenteral therapy, the patients were on a smooth diet, with small doses of antispasmodics and sedatives at times. 'Shock-reaction,' twice very severe, was noted in 7 cases."

A personal letter from Arthur Hurst of London, in regard to the non-specific protein method of treatment, tells of his experiences with many patients treated under that method by a German authority and dismissed as "cured"; but Hurst later observed at operation that the ulcers were as large as before, showing that while the protein "shock" treatment had relieved pain, it had not helped the ulcer, and in fact, had achieved no results that dieting and rest could not have secured.

Eusterman had a similar experience while working in prominent Clinics abroad; patients who had been supposedly cured by protein therapy were found at operation to display no trace of healing. He thinks that very probably none of the other preparations are any more efficacious.

D. M. Rosenberg informs me in a personal communication that he took particular pains to question physicians afflicted with peptic ulcer, who had undergone parenteral treatment, and was told by the majority that they were greatly disappointed with the results. This investigator is thoroughly convinced that peptic ulcer is a chronic disease which in many instances presents spontaneous remission, and that the parenteral method is in no wise superior to orthodox therapy.

Garbat, in a personal letter, states that he has observed in both private and ward practice, the application of duodenal intubation, mucin, "aolan," insulin, "larostidin," etc.; and without criticism of those who advocate these methods, he has concluded that basically, diet is the essential treatment, all other agencies to be used as adjuvants only. He considers it a poor principle for physicians to depend on parenteral methods without diet, because the ultimate care of the ulcer and associated gastritis and the prevention of recurrence, can only be accomplished by dietetic and medicinal methods carried over a period of years. He emphasizes the fact that it takes 6 months to 2 years or more to cure an ulcer and its associated gastritis, if the process is curable; and he rarely speaks of a real *cure* in ulcer.

Regarding the results in peptic ulcer following specific therapy with alleged improvement or cure of the disease, T. R. Brown directs attention to two very significant but sadly neglected facts: first, that uncomplicated ulcer is a self-limited disease, and only the most pernicious form of therapy will prevent it from healing in its self-appointed time; second, we do not know the cause of ulcer, and until we know the primary cause, if such there be, prevention is difficult and treatment often unsatisfactory and symptomatic.

Aaron, of Buffalo, writes me: "As to the parenteral therapy for ulcer, we are not using it at all. We believe its claims are unwarranted and we have had a sufficient number of cases on the hospital Service who have had this treatment. They still have roentgen evidences of ulcer and the symptoms have still persisted. It seems to me that the orthodox method is still the best we have at hand."

A newer method which during the past few years has gained considerable recognition is gastric mucin therapy in the treatment of peptic ulcer. This form of treatment has been particularly lauded by Fogelson, on a basis of Lim and Ivy's work, and in a late article he presents statistics based on questionnaires submitted to clinicians throughout the country, concerning 494 patients with peptic ulcer treated by gastric mucin. The results showed that all symptoms were controlled in 70.5 per cent; partial relief was obtained in 23 per cent, and failure to afford relief in 6.5 per cent. "In 217 patients with intractable ulcer, unable to obtain relief of symptoms by medical management, 69 having had previous surgical procedures, gastric mucin brought about absolute relief in 63.1 per cent, partial relief in 29.4 per cent, and no relief in 7.5 per cent. Because of the limited time for observation, the permanence of the results was not considered."

Ralph C. Brown, Chicago, in a recent letter, says: "I have carried on a very considerable piece of work with animal mucin and have discarded it as a rational method of treatment because of its tremendous secretagogue effect. The acid curve resulting from its administration (following a brief period of acid-neutralization) is exactly superimposable to that obtained by the administration of histamin. I am too profound a believer in the influence of free HCl as a causative agent in the chronicity of ulcer to believe that mucin is the answer to the problem. To sum the matter up, I am old-fashioned and orthodox to a degree in my viewpoint. I know quite well that there are very few peptic ulcers either of the stomach or duodenum which will not heal if the surface of the ulcer can be freed throughout the day and night from the proteolytic action of gastric juice containing definite concentrations of free HCl. The evidence here is overwhelming, especially that obtained by a series of films of large, deeply penetrating gastric ulcers. I could show you hundreds of such cases where we have films made at ten-day intervals showing rapid and progressive disappearance of the lesion. When one can obtain such results by the intelligent and skillful application of such a proven principle, why should he countenance the use of methods which have no scientific background, or at least a questionable scientific background?"

Smithies, after a very thorough clinical study, concluded that mucin was unsatisfactory; administration was difficult with or without food; the dosage was too arbitrary, and the effects not good enough to justify the high cost and the confidence placed in the remedy by over-optimistic patients. Moreover, some cases displayed disquieting toxic symptoms after its application.

Eusterman, also Henning and Norpoth, have observed favorable response in a number of cases treated by this method. However, it has never appealed to me, and after reading unfavorable reports and being

personally informed by responsible and capable investigators of their disappointment in its results, I have never become sufficiently interested to adopt it as a therapeutic measure in peptic ulcer.

#### AUTHOR'S ULCER REGIME

The *orthodox or conservative method* in peptic ulcer therapy, of which I continue to be an advocate, I shall outline in brief; however, it is to be thoroughly understood that individualization in each case is practised as regards hygiene, both physical and mental; in diet, and in medication; indeed, very few cases are treated in an identical manner.

The procedure in this method, reduced to essentials, is as follows: *Hygiene*: rest, physical and mental; physical rest includes both general bodily rest, and rest of the digestive tract; it must be realized, however, that a definite number of individuals respond far more satisfactorily when allowed to be up and about, attending to their daily duties, than when confined to bed, since the latter may be conducive of worry, irritation and apprehension about household or business duties. Recently there has been accorded a rightful recognition of the effect of mental states in these cases; therefore, appropriate gestures in this domain must receive due consideration; in short, the patient must be studied as an economic, as well as a physiologic, entity. *Local heat or cold* must always be considered. The *elimination of all foci of infection* should be a routine matter; thorough investigation of every organ, group of organs, and the tissues, is involved in this.

*Diet* begins with small amounts of bland liquids, not too frequently applied; various views exist as to the efficacy of milk and cream, or watery carbohydrates, this latter method being termed by Smithies "the physiological rest" method. I have found a combination of both most effectual. We should individualize in our therapy, and if an individual has a true idiosyncrasy toward certain articles of diet, these should be eliminated; otherwise the greater the variety of foods available, the more satisfactory the course for the patient and the doctor. According to the response of the patient, a gradual increase in amount, consistency and variety of food is carried out. The computation of the caloric value of the daily food and vitamin balance, should never be neglected. One of the most costly mistakes the average physician makes, is failing to insist upon the most careful dietetic regime being continued for at least 12 months; it takes moral courage, but it should be done; he should also insist that the patient bear always in mind that the digestive tract is the weak link, and will necessitate continual caution in regard to food and the details of daily life.

The *medicinal phase* of the treatment should be as simple as possible. I do not approve of the hourly application of drugs, preferring in the usual case, intervals of two or three hours, from early morning until bedtime; here again individualization is urged. We have always had, and continue to have, much faith in belladonna or atropine. But alas, now comes Bastedo, stating in a recent paper, that our views as to the efficacy of these remedies are quite erroneous, and that the dosage used is ineffectual; that to produce the results we desire, it would be necessary to give an amount which would be poisonous and very dangerous! It does seem that our troubles never will cease!

Various combinations of the alkalis: sodium bicarbonate, calcium carbonate, magnesia, have, in our hands, in sufficiently large dosage, proved most efficacious; in patients with obstructive and kidney complications, the possibility of alkalosis must receive consideration; but we have never encountered such a complication. In obstinate cases, duodenal feeding is used by some authorities, also nightly aspiration of the gastric contents.

The so called neutral salts marketed as "Triophos," "Tri-Calsate," "Alucol," have been highly recommended; frankly, however, I have never been convinced that they possess worthwhile superiority over the homely alkalis which I have enumerated.

The mild, stimulating type of laxative indicated,—magnesia, mineral oil, liquid agar, cascara and enemata,—are the most satisfactory and effectual.

The *upbuilding phase of therapy* is best accomplished by the use of nourishing food, well-balanced dietary, as regards vitamins and caloric value; fresh air, sunshine, rest, recreation, vacation, relaxation both mental and physical. Massage; physiotherapy, light therapy, are often most valuable if applied by experts; hematinic agents, iron, liver, arsenic per os or hypo. In short, common-sense therapy based upon physiologic facts so far as we know them.

In 1925, Smithies presented a very detailed report showing the result of the "physiologic rest method" in peptic ulcer. It will be possible to enumerate only a few of his results, which were obtained by a very thorough clinical investigation. He emphasized the too frequently overlooked fact that peptic ulcer is often, viscerally, a self-limited ailment of peculiar "periodicity," whose "natural" remissions are too generally regarded as dependent on special modes of management. In this attitude I heartily concur.

The material analyzed in his study comprised 470 patients with ulcers as follows: 128 wholly gastric; 36 pyloroduodenal; 306 duodenal; all were observed for a period of 10 years; he makes the very significant statement that when a clinician follows any type of therapeutic management for any particular form of ailment in a considerable group of patients over a number of years, he is in better position to secure the desired results than are those to whom the procedure is new, or who manage only an occasional patient. In his series, the average hospitalization was 28 days; bed confinement averaged less than 9 days; in 40 per cent all pain had disappeared within 48 hours of beginning the treatment; an added 33 per cent experienced pain relief within 48 hours; 8 per cent required 72 hours; 15 per cent almost 96 hours; in approximately 4 per cent it was necessary to relieve pain by opiates, this last group comprising those with complication. A total of 81 per cent were subjectively comfortable in 3 days or less. Of 41 per cent of the cases exhibiting positive occult blood tests when treatment was begun, at the end of 5 days, 92 per cent of the stools were bloodfree. 7 of the cases (1.5 per cent) went into actual perforation. In 66 patients who came to laparotomy for numerous intra-abdominal lesions, following institution of his ulcer management, completely healed scars were demonstrated in 54, or approximately 82 per cent. Roentgen-ray proof of healing was shown in 94 cases by disappearance of local ulcer, tender areas on palpation during fluoroscopy, or by absence of inferential motor phenomena

characteristic of active ulceration. For the whole series, recurrences were noted in 14 per cent (66 cases); the recurrences were of an ailment like the primary one, and roentgen-ray proof was available showing that the visceral upset was at the site of the initial lesion. After a very thorough study of the 470 cases, Smithies was convinced of the cessation of the ulcer process in 361, or 77 per cent.

In a recent personal communication, Smithies calls attention to an important fact often ignored,—that the roentgen deformity following the healing of an ulcer is at times greater than it was before the healing, due to accumulation of protective scar tissue; and in this connection, marked or complete obstruction of the stomach or duodenum may be brought about; also that malformation of the stomach may result from vigorous scar response in an attempt at healing; in such changes, the ulcer may heal; but the resulting deformity is so marked that corrective surgery becomes imperative; thus we see that the healing of a peptic ulcer does not always mean a stomach or duodenum of perfect or normal contour.

As a further proof of the efficacy of the conservative, orthodox rest-method, I desire to present the results of a thorough, most painstaking and convincing piece of investigative work by Sara Jordan and Lyman Boynton; they state that the rate of healing could be, and was, estimated by the diminution in size, and disappearance of, the X-ray defect on 41 ulcers of the media or lesser curvature, and in 6 prepyloric lesions. In 13 cases complete healing of the ulcer had occurred before the patients left the hospital, *i.e.*, within 21 to 28 days after the beginning of treatment, while 19 showed by diminution in size of the defect, satisfactory evidence of healing before leaving the hospital, and in 4 to 10 weeks after discharge showed complete disappearance of the niche. Of the 6 prepyloric lesions, 3 were originally diagnosed as ulcer, but were operated upon because of persistent X-ray defect and suspicion of malignancy; 2 were completely healed by X-ray evidence, within 7 weeks of the first observation; one was apparently healed and could not be controlled for further observation until 9 months later, when he returned with a carcinoma involving the ulcer, and it was a question as to the origin of the malignancy in the stomach or the pancreas. As to the therapy, Jordan and Boynton say: "We use the Sippy treatment or some modification of it, but we do not always use alkalis in these stomach cases; sometimes rest in bed, careful diet, freedom from worry, are adequate, the rest particularly." Thus we observe a series of perfectly controlled cases, 47 in number, in which it was proven that healing of the ulcer occurred in 35, approximately 75 per cent, within 10 weeks after the institution of conservative rest type of treatment.

I challenge any of the proponents of the various parenteral methods of therapy to present indisputable evidence which could equal these splendid and definitely proved achievements.

A recent and most comprehensive clinical study has been presented by Emery and Monroe; in which they call attention to the continued unsatisfactory management of peptic ulcer, due largely, they believe, to our ignorance regarding its etiology; in this regard, they quote Brooks in his statement that we should not speak of the *cure* of peptic ulcer, but rather of mitigation of certain of its signs and symptoms, until the cause of



peptic ulcer has been definitely demonstrated. These authors lay great emphasis on the fact that symptoms fluctuate with spontaneous remissions and relapses, the intervals ranging from weeks to many years; in 500 patients who were particularly questioned, the remissions seemed definitely spontaneous in 131.

It seems pertinent to inquire as to the dependability of dogmatic statements regarding the efficacy of this or that type of treatment when so large a number show spontaneous remissions; and it is interesting as well as enlightening to note that these authors have long since ceased to entertain the notion that one form of therapy is far superior to all others, and that they call attention to the need of individualization in the supervision of each case. It is very significant, albeit discouraging, to note their belief that the longer one follows patients with peptic ulcer, the fewer are medical cures he can claim. They are convinced that peptic ulcer is primarily a medical problem, and that a strict Sippy regime is the best medical solution; they have used and discarded mucin because of the unsatisfactory results; further, they feel that while surgery is at times indispensable, even life-saving, it does not cure the disease or alter its tendency to persist. They note that if patients are allowed to revert to their usual habits, they will relapse as frequently after a Sippy regime as any other, and that none of the present medical or surgical gestures do more than assist in bringing about remissions. Their results of medical treatment, after 3 to 6 years observations of 1,085 cases show: No symptoms, 13.7 per cent; very few symptoms, 36.5 per cent; definite improvement, 30.8 per cent; improvement, 6.3 per cent; no improvement, 12.5 per cent. However, the cases reported by Emery and Monroe did not represent their own personal experiences in management; the majority of the cases were taken from hospital records. The patients had been treated by numerous physicians and, doubtless, by several regimens of therapy.

I was interested in their admonition that one must treat the whole patient, and not the ulcer alone. In a final summary of a group of 1,258 patients receiving medical and surgical care, they consider that 81 per cent were successfully treated.

### SUMMARY

I have no hesitancy whatsoever in stating that to date my experience in the use of parenteral therapy has been overwhelmingly unsuccessful and disappointing; so far as I am able to see, its only virtue is its antispasmodic effect, and this seems to me no more striking than that obtained by rest of body, mind, and digestive tract, as already outlined in the orthodox rest method. Be that as it may, I still maintain an open mind and watchful attitude, and shall continue

to follow with intense interest the work which others are now carrying on with this radical method; if at a later date I am convinced of its superiority over the conservative therapy which I now support and use, I shall hasten to modify my present views.

It is in matters of moment such as this question of therapy of peptic ulcer, that criticism is most valuable; for from the collision of adverse opinion there flashes the spark of truth which, fed by eager devotion for knowledge, becomes a revealing flame.

I am not reactionary, for I whole-heartedly realize the need of the pioneering spirit, above all in the field of medicine; and inquisitive and independent thought is to be encouraged in order that we may be freed from the shackles of traditional assumptions; every idea has a right to existence, and intolerance and bigotry should be banished to the limbo of forgotten evils, but it is quite possible for progress to be made in a rational manner with the establishment of a mutual understanding of our problems, if we consider it a bounden duty to listen to both sides of every question with thoughtful attention.

However, as the medical profession has been only too prone to accept uncritically and to place a benediction upon, the attractive and the spectacular, every theory and procedure should henceforth be required to present properly conducted and adequately supervised laboratory and clinical research in substantiation of its claim.

I wish to place myself in that group of observers who look upon peptic ulcer as a chronic disease, the etiologic factor or factors of which have so far not been discovered; a disease which is characterized by spontaneous remissions, and thereby deprives us of the right to state unequivocally that it is cured. No matter what remedies have been applied, a large number of cases will always give favorable results; the statistics thus far published to support the claim that parenteral therapy has established its superiority over that of physiological rest, or orthodox method, do not bear out this claim, since they are inadequate in number, and the period of time over which the cases have been observed has not been sufficiently prolonged to prove permanent results.

Finally, the whole question of therapy really becomes more and more of a problem, and one wonders just how much is really accomplished by our efforts along the lines of hygiene, diet and medication. I am by no means a therapeutic nihilist, but after much experience over many years, I am moved to inquire of myself if there may not be a germ of truth in the witticism: "Medicine is the art or science of amusing a sick man with frivolous speculations about his disorder, and temporizing ingeniously until nature either kills or cures him."

### REFERENCES

- Aron, E.: *Strasbourg Med.*, 93:731, 1933.  
 Aron, E. and Welter, A. G.: *Compt. Rend. Soc. Biol.*, 112:15-530, 1935.  
 Atkinson, A. J.: *J. A. M. A.*, 98:1153, 1932.  
 Babbitt, B. P., and Komarov, S. A.: *Canad. M. A. J.*, 27:463, 1933.  
 Berger: *Munch. Med. Wochschr.*, 27:924, 1924.  
 Blum, P.: *Bull. Gen. de Therap.*, 243, 1933.  
 Brown, T. R.: *Amer. Jour. Digest. Dis. and Nutrit.*, Sept., 1935.  
 Bulmer, E.: *Lancet*, 2:1276, 1934.  
 Fadd, J. T.: *Amer. Jour. Digest. Dis. and Nutrit.*, Sept., 1935.  
 Emery, E. S., Jr., and Monroe, R. T.: *Peptic Ulcer. Arch. Intern. Med.*, 57, Feb., 1935.  
 Engel, A.: *Arch. für Verdauungs-Krankh.*, Berlin, 56:237, 1934.  
 Foye, S. J.: *Arch. Intern. Med.*, 35, Jan., 1935.  
 Grote and Bergmann: *Zentralbl. f. Inn. Med.*, 45:337, 1924.  
 Hessel, G.: *Munch. Med. Wochschr.*, 81:1599, 1934.  
 Heller: *Wien. Klin. Wochschr.*, 34:223, 1921.  
 Ivy, A. C.: *Nebraska St. M. J.*, 17:317, 1932.  
 Jordan, S. M., and Boynton, L. C.: *Trans. of the Amer. Ther. Soc.*, 31, 1934.  
 Kalk, H.: *Klin. Wochschr.*, 28:1310, 1923.  
 Kaulman, J.: *Am. Jour. Med. Sci.*, 135:207, 1908.  
 Lenormand, J.: *Gaz. des Hôpitaux*, 107:256, 1934.  
 Lim, R. K. S.: *Am. Jour. Physiol.*, 69:318, 1924.  
 Mann, F. C.: *Am. Jour. Surg.*, 7:453, 1920.  
 Mann, F. C. et al.: *J. A. M. A.*, 73:878, 1919. *Am. Jour. Surg.*, 75:208, 1922, 27:409, 1923.  
 Martin, Lay: *Arch. Intern. Med.*, 43:299, 1929.  
 Martin, Lay: *Ann. Intern. Med.*, 6, No. 6, Nov., 1932.  
 Mitchell and Hamilton: *Biochem. of the Amino-Acids. Monograph Series No. 4*.  
 Pribram: *Med. Klin.*, 18, 1922. *Klin. Wochschr.*, 2:2112, 1923. *Deutsch. Med. Wochschr.*, 51:141, 1925.  
 Schiff and Norris: *Jour. Med.*, June, 1931.  
 Smithlee, F.: *Amer. Jour. Surg.*, 18, No. 2, Nov., 1932.  
 Volini and McLaughlin: *Med. Record*, April 17, 1935.  
 Von Friedrich: *Arch. f. Verdauungs-Krankh.*, 24:76, 1925.



## SECTION VII—Surgery of the Lower Colon and Rectum

### Lymphopathia Venerea: A Clinical Survey

By

COLLIER F. MARTIN, M.D., F.A.C.S.  
PHILADELPHIA, PENNSYLVANIA

THIRTY years ago I began working in the Rectal Clinic of our good friend, the late Lewis T. Adler, Jr. Since that time I have served with the Philadelphia Polyclinic Hospital and the Medical Department of Temple University, and in 1918 returned to the Polyclinic, then known as the Graduate Hospital of the Medical Department of the University of Pennsylvania. During all of these years many cases of rectal stricture were encountered which in early days were ascribed to syphilis, gonorrhea, colitis and those of unknown etiology. It was noted that the majority of these cases of stricture occurred in the female and that the negress seemed particularly susceptible. In 1932 my attention was called to the fact that many of these strictures, with their curious sequelae, might be due to the disease at that time called Lymphogranuloma Inguinalis, now called *lymphopathia venerea*.

It is my purpose in this short paper simply to review the work and some of its problems which we met in the routine treatment of these cases, leaving out much of the historical detail.

During the past three years many articles upon this subject have appeared in American literature, although hundreds of articles have been published abroad previous to this date. Just at present the medical profession of the United States seems to be becoming lymphopathia minded, so that we may expect a flood of literature during the next few months or years.

The term "*lymphogranuloma inguinalis*" given to the disease recognized by Nicholas and Favre in 1913 is so frequently confused with "*granuloma inguinalis*" that in 1932 Wolf and Sulzberger substituted the term "*lymphopathia venerea*," believing that this term more fully described the pathology concerned.

The disease itself is believed to be produced by a filterable virus and is manifested in the male by the presence of a suppurative or non-suppurative adenitis. Various inflammatory conditions of the rectum and anus, frequently evidenced as multiple ano-rectal fistulae, recto-vaginal fistulae, and the formation of stricture of the rectum, more frequently encountered in the female. Such conditions as genito-rectal elephantiasis and esthiomone are of frequent occurrence both in the male and female. In 1925 Frei developed a skin test which was, and is, believed to be specific.

The antigen he employed was made from pus secured from an inguinal bubo. While we have used Frei's technique in preparing this test, and even have made use of pathologic tissue taken from a positive case, we have always felt that there was no way to standardize this substance for its activity.

While the disease is not confined to the Negro race, the Negro probably shows more variations in pathology than the white. Whether this be due to the co-existence of other venereal infections or to racial differences described by Rosser as the "fibro-plastic diathesis" would be hard to prove. Rosser probably had in mind a tendency toward keloidal changes in the skin of the Negro and the tendency to rather massive granulomatous changes along the lines of the lymphatics in the deeper tissues. In 1924 the writer used the term "Negromata" to describe these peculiar granulomatous tumors.

In Philadelphia we have a very large Negro population, practically 11%, in other words, nearly 220,000. New York City has but 4.4%, and in Chicago practically 6% are blacks. While Philadelphia is the third city in population, and also is third in the total number of blacks, it stands first in saturation. In our rectal clinic, situated almost in the center of the Negro district, there is ample opportunity to meet many of these pathologic cases. In other countries, such as in Europe or Asia, more cases may be found among the white, probably due to the fact that there the colored race is not so much in evidence.

Stricture of the rectum is more frequently encountered in the female, therefore this sex predominates in our clinic, while in the male the primary penile sore associated with inguinal adenitis is more frequently seen. Due to the mode of transmission, it is unusual to find a patient without some other associated venereal disease. This is true among the blacks and the lower class of white prostitutes. In spite of the fact that the pus employed to make antigens has been taken from patients with one or more additional venereal diseases, apparently their presence did not influence the specificity of the Frei reaction. So far we have obtained positive reactions in 96.7% of the cases.

Since inguinal adenitis was seen rarely in the female it was found necessary to obtain the cooperation of the Departments of Dermatology and Urology to procure pus for the production of our antigens. In the male the primary lesion was met with as a penile sore, herpetiform or vesicular in type, resembling

somewhat the so-called "hard chancre." The primary infection was quickly followed by suppuration of the inguinal glands, either unilateral or bilateral. These glands would break down, discharge, heal, break down, discharge, and heal, *ad infinitum*. The longer this condition progressed, the more the induration of the overlying tissues became apparent and the later scars became contracted, probably due to the fusing of the layers of underlying tissues. Following excision of these glands, or following simple palliative treatment, it was not unusual to notice marked thickening, hypertrophy or even elephantiasis of the genital organs.

The female obtaining her infection from the male develops the primary sore in the fourchette, the posterior vaginal wall, or the posterior lip of the cervix. As the primary sore is non-painful and is not accompanied by any marked discharge, it is not to be wondered at, that it is overlooked in this sex. Instead of the infection traveling to the inguinal glands, it is transferred to the para- or perirectal lymphatics, affecting the massive groups of lymphatics traveling to the anal nodes of Gerota. This peri- or pararectal lymphangitis is characterized by a rather marked infiltration of round cells or inflammatory cells which later become organized into dense fibrous tissue. In these areas of infected tissues, frequently are to be noted miliary abscesses and it is these multiple foci that probably account for the repeated and multiple points of massive induration and suppuration. Because of this inflammatory deposit, stricture formation occurs rather early, and with this stricture formation and with this interference in the blood supply and in nutrition, necrosis of the lining of the rectal wall occurs rather early. When the stricture stage is reached, there seems to be no deformity or complication which may not be present—abscesses, fistulas, hypertrophies of the anal and urogenital tissues, and even elephantiasis. Many cases show marked deformities of the genito-anal areas, frequently described as *lupus excedens* or *esthiomone*. Many writers have blamed the elephantiasis and deformities upon the destruction of the lymphatics following operative interference, but it may be just as true that the disease itself having caused obliteration of these vessels would produced the same effect.

During the past two years we have on our records about 155 cases of *lymphopathia venerea*. Some of these cases were observed by members of our Proctologic Staff also connected with other hospitals, notably W. O. Hermance, at the Woman's College Hospital, J. C. Werner, at Mt. Sinai, J. D. Schofield, at Hahnenmann, and Harry E. Bacon, at St. Luke's Hospital. Also, Bacon has studied some cases at the Temple University Hospital, in the service of Dr. H. Z. Hibshman.

With this cooperation from outside and with the close contacts within our School, it has been possible to gain some idea of the prevalence of this disease. As the majority of patients with rectal pathology from *lymphopathia venerea* occur in women, this sex must predominate in a rectal clinic. Also, as inguinal adenitis is comparatively rare in the female, we are forced to obtain the pus for antigens from the Urologic Service. Frei and others have insisted that the pus for

this antigen must be obtained from a patient free from syphilis, gonorrhea, soft chancre, tuberculosis, and other diseases which may produce specific or non-specific allergic skin reactions. This would seem like looking for virtue in Sodom and Gomorrah, as we have been thoroughly impressed with the fact that the individuals of the Negro race carry about every variety of infection known to Venus and her gentlemen friends.

We have been rather in doubt as to the standardization of, and the specificity of, our Frei antigens, since during the past few months we have simply sterilized them and not preserved them with any antiseptic, feeling that even the addition of carbolic acid might produce a local skin reaction. Formerly we made a control antigen from macerated inguinal glands obtained from an apparently normal individual. As the control antigen never showed a positive reaction, this method was abandoned. While the reaction obtained from the antigen as prepared by our laboratories was apparently satisfactory, yet the possibility of contamination, or the delayed growth of bacteria already present in the antigen was felt to raise some doubt as to our readings. However, Bacon reports that 264 cutaneous tests with these antigens were 100% negative in cases where *lymphopathia venerea* was unsuspected. Homer I. Silvers reports that 100 injections made upon clinic patients in the Atlantic City Hospital, not suspected to have this disease, were negative. In the Urologic Clinics 200 tests were made and 19 gave a positive reaction, 18 occurring in the Negro race. All of these cases had ano-rectal symptomatology and gross pathology. This would apparently indicate that our antigens were not contaminated. At present we are trying to standardize our Frei antigen.

Our clinics are fairly well filled with Negro patients in all stages of the disease. We are greatly impressed with the fact that, like the poor, they are always with us. One case, Roberta M., has been operated upon once, twice, or more times, per year, for the past thirty years. She has been treated for everything from alopecia to syphilis and gives a very positive reaction of the Frei antigen. I may add that tissue removed from her vulva was macerated and made into an antigen which apparently was extremely active.

Our cases seem to have every possible complication, such as inguinal adenitis, elephantiasis, esthiomone, rhagades, and almost every deformity known to woman and occasionally transferred to man. The diseased tissue is not moth-eaten, but rat-bitten in appearance, showing multiple sinuses of the vulva, perineum, perirectal tissue, and even, in many cases, recto-vaginal fistulae.

The rectal strictures found in most of these patients tend rather to be extensive in their encroachment upon the rectal and perirectal tissues. Vaginal examination to the palpating finger may reveal the dense inflammatory mass, feeling much like a piece of garden hose, which replaces the normal rectum. The entire pelvis below the reflection of the pelvic peritoneum is filled with a dense deposit of this peculiar granulomatous tissue. Local examination in many cases shows a patulous anal orifice, anal rhagades, and a papillomatous proliferative change of the anal and lower rectal tissues. The stricture, if present, usually is above the

ano-rectal line, extending from one to ten centimeters upward, of a calibre which may admit the index finger, but which usually will not admit the passage of an ordinary lead pencil. The mucous membrane frequently is absent in the greater portion of the rectum. The tissue is unyielding, undilatable, and does not give the impression of a massive infiltration of new tissue such as found in cases affected with malignancy. To use a homely comparison, I would say that the malignant stricture rather "jumps at you," while the lymphopathic stricture will not let you pass.

The question of treatment may not be considered in this paper because of time. Suffice it to say that, so far, nothing has been discovered that has given any relief of the obstruction from a therapeutic standpoint. The mechanical relief of obstruction is best obtained by colostomy, which may or may not be followed by extirpation of the total mass. All other operations have been found ineffective. I believe that the removal of a rectum infiltrated with this granulomatous mass presents a far greater mechanical problem than in a case suffering from carcinoma. I cannot avoid feeling that *lymphopathia venerea* is not simply a local disease, but that it is a very generalized infection associated with massive local pathology and deformities at the point of primary spread. There seems to be no picture which uniformly represents the changes encountered, and there seems to be no limit to the variety of gross tissue changes and no end to the many complications met. To me, other venereal diseases, even syphilis, would seem rather easy to describe, compared with the multiplicity of complications met with in *lymphopathia venerea*. Every form of medical treatment has been tried—injections of tartar emetic, "Fouadin," non-specific proteins, and intravenous, cutaneous and subcutaneous injections of the Frei antigen, and even intravenous injections of hydrochloric acid, 1 to 1500. So far, little or no improvement has been noted. Locally, surgical measures such as dilatation, proctotomy, carbon dioxide snow, and the Jelks' operation, have given poor results. A permanent colostomy apparently is our best procedure. Should the case present a good surgical risk, both locally and symptomatically, the colostomy may be followed by a complete extirpation. It must not be overlooked that these patients suffer with multiple rectal and perirectal infections, a somewhat lowered vitality, and frequently they have a rather pronounced anemia. At present the mortality will probably exceed that following extirpation for carcinoma.

Undoubtedly, our patients belong to the lower stratum of society and at the present time are unemployed, and if encouraged, will remain so. It is easily to be seen that the problem presents a very important study in cost to a community. Practically all of these cases are admitted to our wards, with no hope of the hospital receiving one cent of remuneration, and they are treated in our clinics for exactly the same fee. Once the diagnoses are made, we know that these patients will probably be visitors to the clinic and inmates of the hospital as long as they live. They

certainly are not welcome in our private offices and they take up an immense amount of our time in the free clinic. In Philadelphia, New York, and other large cities which have a large Negro population, the cost to the community must be excessive.

While there are very stringent rules for the examination of help employed in restaurants and hotels, *lymphopathia venerea* has been unrecognized and undiagnosed. As it seems to be a contact disease, it is a grave question as to how easily it may be transmitted by other means than by sexual intercourse. Undoubtedly, some cases have been reported of mouth infection. The inference is that abnormal practices may be blamed, but who knows? This probably is a more or less generalized, world-wide disease.

In Europe, particularly in Sweden, Germany, France and Roumania, the rapid increase of cases appearing in their hospitals has occasioned much alarm. As the patients nearly all belong to the lower stratum of society, are not self-supporting, and are dependent upon the dole, the problem is an important one. Hospitals in Europe, and I may say in America, are certainly in need of money, and any extra burden placed upon them certainly must be considered. Sweden is seriously considering including *lymphopathia venerea* among the venereal diseases to be reported under their extremely drastic law, and has requested cooperation from Germany, France and Roumania. In this country, undoubtedly cases are increasing, the largest number being found in the colored race because of their rather promiscuous living conditions and lack of intelligent cooperation with medical authorities.

During the World War while prophylactic stations were established in about every third house in the towns frequented by soldiers, the mere fact that after voluntarily accepting this proper treatment the soldier's name was reported to his commander and recorded on his permanent record, soon resulted in no reports being turned in and a tremendous increase in the spread of venereal disease. Many of our colored patients belong to the class working in kitchens and are more or less directly concerned in handling food. Should they be reported they would lose their jobs. The result is obvious. They certainly will never appear for examination as long as they are fit to work.

Apparently we are confronted with a disease, which is wide-spread, of extreme chronicity and devastating in its effects and eventually fatal in termination. Very shortly we will agree with the European medical authorities that we are confronted with an incurable disease far worse than syphilis and ranking very close to malignancy in its operability. Apparently the only efficient means of control of this disease lies in preventive medicine. The fact that the male rarely reports early and the female never, would place them in the class of incurability. Very early treatment might be effective. The passage of more legal restrictions might or might not be useful. Should these be enforced as laxly as the present ones on other venereal diseases, little may be expected.

# Recto-Urethral Fistula: An Operation For Its Cure\*

By

CECIL D. GASTON, M.D., F.A.C.S.

and

A. B. LEE, M.D.

BIRMINGHAM, ALABAMA

IN 1913 Young and Stone (1) presented an operation for the radical cure of post-operative recto-urethral fistula with a report of three cases. In a second publication (2) four years later, these authors added eight additional cases, making a total of eleven, all but one of which were successful. Later, Davis (3) reported three successful results by this method. Briefly, the Young-Stone operation is a radical anorectal dissection, the prime feature of which compares with an extensive Whitehead hemorrhoidal operation, where a cuff of the rectum is mobilized and drawn down far enough to be amputated above the fistulous opening. Other essential features are suprapubic drainage, urethral closure, and the bringing together

lithotomy. As a sequel to suprapubic prostatectomy, Bayer (4) reports one case, Stark (5) reports one case, Young and Davis (6) report two cases and Graves (7) reports one case. The subject under consideration records an additional or sixth case following suprapubic prostatectomy.

The diagnosis is easily made. Passage of gas per urethram and urine per rectum is the characteristic feature. With the history of a previous operation, little doubt exists as to the condition. Rectal examination reveals an opening in the mid-anterior rectal wall, within one or two centimeters above the sphincter ani, communicating directly with either the membranous or the prostatic urethra, usually the former.



Fig. 1. The position for patient. A modified Sims' retractor is placed into the angle of the posterior proctotomy.

of the fascia and levator fibers in the midline as an additional barrier between urethra and rectum.

In the attempt to cure this tragically surgical complication or sequel, a review of the literature discloses eloquent proof of the difficulties and failures encountered. The primary purpose of this paper is to describe a simplified operative technique with adequate field exposure and to relate the result of its clinical application. An exhaustive consideration of the lesion itself will not be attempted. It is to be emphasized that the type of case under consideration does not include those fistulae of tuberculous or malignant origin, but only those occurring as a result of surgical trauma.

The majority of recto-urethral fistulae are unfortunate results of perineal prostatectomy or perineal

In many cases, a communicating perineal fistula presents.

## CASE REPORT

The operation under discussion was performed upon a white male of sixty years. The history of this fistula dates back to a suprapubic prostatectomy that was performed September 15, 1933. While straining at stool eleven days later, the tip of the urethral catheter presented through the anus. Following this accident, the urethral catheter was removed and a suprapubic tube was reinserted. Gas and feces passed with the urine through the suprapubic tube. Similarly, urine passed per rectum and fecal products, chiefly gas, passed per urethram. Rectal examination showed an opening into the membranous urethra large enough to admit the tip of the little finger. The margin of the opening was well defined and densely infiltrated. Suprapubic drainage was continued for eleven weeks, when the operation for closure of the fistula was performed under spinal anesthesia.

\*Read before American Proctologic Society, 35th Annual Meeting, Atlantic City, New Jersey, June 10-11, 1935.  
Submitted November 8, 1935.

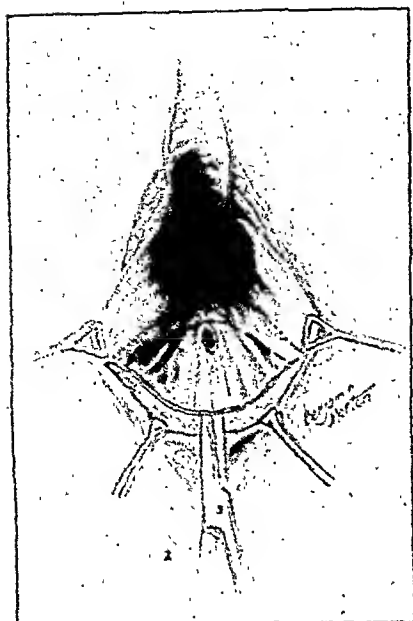


Fig. 2. This shows the field exposure with fistulous opening. Anal incision is completed. Dashes show the approximate line of amputation. Dots show the uppermost line of undercutting.

**Operation:** A clear concept of the technique of dissection and repair is best gained by a study of the illustrations. The patient was placed in the ventral-prone posture, hips were elevated 15 centimeters, the body plane was lowered 30 degrees, the thighs and legs were lowered to a plane just below the horizontal (8) (Fig. 1). A complete posterior proctotomy was first performed. A Pennington forceps was placed at the right and left anal points. Posterior retraction was gained with a modified Sims' retractor, the blade being inserted into the depths of the posterior incision. Complete exposure of a bloodless field was thus obtained. Between the Pennington forceps, an incision was made anteriorly, a few millimeters proximal to the anal verge (Fig. 2). From this incision, anal integument and rectal mucosa were dissected upward to

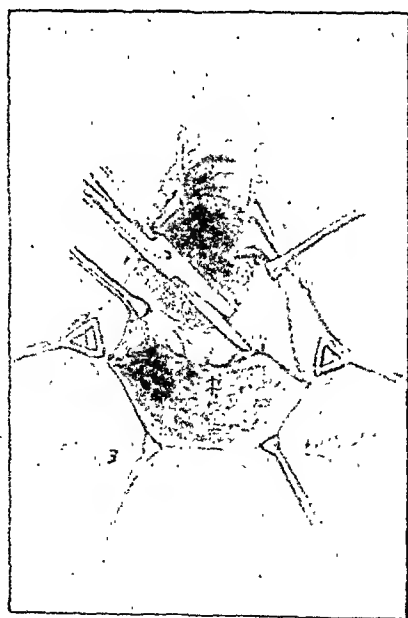


Fig. 3. Amputation of flap. Fistula is closed with interrupted catgut sutures following excision of fistulous margin. Levator fibers with coverings are to be apposed over this closure.

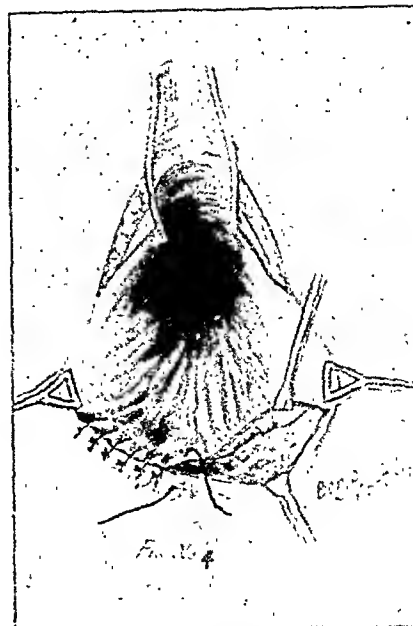


Fig. 4. The flap has been mobilized, drawn into apposition with incised anal skin and is partially approximated with sutures of interrupted catgut. Black space at left angle represents the small redundant fold of mobilized flap.

form an apron of tissue. Following exposure of the sphincter ani, this muscle was retracted forward with an Allis forceps, the mucosa was grasped deeply and the planes of cleavage were followed upward. Sharp dissection was found to be necessary about the fistulous tract. The apron of tissue was mobilized upward to a midline point approximately 2.5 centimeters above the fistulous opening, the upper border of the flap representing a sharp upward curve. The flap was then amputated just proximal to the fistulous opening, the line of amputation passing from the left angle to the right angle of wound. The margin of urethral opening was excised and closure was accurately accomplished over a retention catheter with interrupted sutures of No. 0 chromic catgut (Fig. 3). Several interrupted sutures of No. 1 chromic catgut were then placed deeply and laterally to bring into apposition

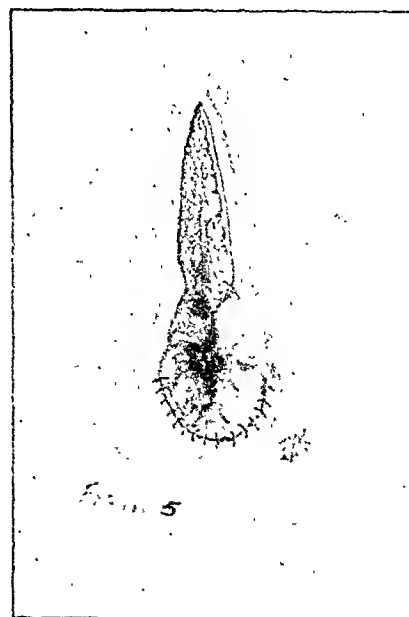


Fig. 5. This shows the appearance of field upon conclusion of operation. Note the absence of packing to prevent incontinence.

the levator ani elements as an additional barrier. Following complete hemostasis the margin of the anterior mobilized flap was sutured, without tension, to the skin margin with interrupted sutures of No. 0 chromic catgut. These sutures were inserted in such a fashion as to leave a slight redundancy of the flap at each outer angle of the wound to provide drainage (Fig. 4). Figure 5 shows the appearance of the field upon completion of operation. Several strips of rubber tissue were placed through the anal canal to aid in the maintenance of rectal decompression. Throughout the operation the acetone-alcoholic preparation of mercurochrome was generously used.

**Post-operative course:** Adequate post-operative care is imperative. In this case dressings were performed three times daily. An effort was made to approach a dry post-operative field. Mineral oil was administered nightly, beginning the night following the operation. On the fourth post-operative day a spontaneous bowel movement occurred. The urethral catheter was removed on the sixth post-operative day. Three days later much of the urine was passed per urethram. On the fifteenth post-operative day, the suprapubic tube was removed and six days later the suprapubic opening closed. Healing continued without tissue break-down. The patient was discharged on the twenty-third post-operative day.

Six months later, the patient was readmitted to the hospital for correction of a moderate anterior mucosal eversion. The following day, under caudal anesthesia, the rectal mucosa lining anterior anal canal was dissected away. The wound was left open to heal by granulation and epithelialization. An examination, July 21, 1934, demonstrated a complete anatomic and functional recovery.

There was neither complaint nor evidence of anal incontinence. A No. 16 F., urethral sound was passed without difficulty. This patient now holds a responsible position without an indication of former physical difficulty.

In this paper our purpose is to present the following data:

1. A brief discussion of traumatic recto-urethral fistula.
2. To urge the employment of an operative posture that presents a complete and bloodless field exposure.
3. To suggest that the usual wound break-down following repair of these cases comes from the rectal rather than the urethral phase. The mass of literature on this subject reveals that an attempt to cure the lesion usually has been and is considered a general surgical or genito-urinary problem. Apparently slight attention is directed to the rectal side of the case. Of prime importance in the prevention of wound break-down is the maintenance of rectal decompression. This is best obtained through employment of a posterior proctotomy with a follow-up attempt to encourage effortless bowel movements.
4. To submit evidence that this type of case justifies the cooperative efforts of the genito-urinary and proctologic surgeon.
5. To present a simplified technique for the cure of a select type of recto-urethral fistula.
6. To record a sixth case of recto-urethral fistula following suprapubic prostatectomy.

#### REFERENCES

1. Young, H. H., and Stone, Harvey B.: An operation for urethro-rectal fistula; report of 3 cases. *Tr. Am. Assn. Genito-Urin. Surg.*, N. Y., VIII, 270-275, 1913.
2. Idem: The operative treatment of urethro-rectal fistula; presentation of a method of radical cure. *J. Urol.*, Balt., I, 280-317, 1917.
3. Davis, E. G.: The Young-Stone operation for urethro-rectal fistula; report of 3 cases. *S., G. O. Chicago*, XXXII, 225-231, 1921.
4. Bayer, Carl: Secondary vesico-urethro-rectal fistula following trans-vesical prostatectomy. *Zentralbl. f. Chir.*, Leipzig, I, 1068-1089, 1923.
5. Stark, E.: Secondary vesico-urethro-rectal fistula after transvesical prostatectomy. *Zentralbl. f. Chir.*, Leipzig, I, 389-391, 1923.
6. Young, H. H., and Davis, David M.: *Young's Practice of Urology*. Phila. and London, W. B. Saunders & Co., II, p. 693, 1926.
7. Grimes, R. C.: Deep recto-urethral fistula following suprapubic prostatectomy, cured by three-stage operation. *Tr. Am. Assn. Genito-Urin. Surgeons*, XXIII, 431-436, 1930. Also: *J. Urol.*, XXV, 101-106, 1931.
8. Gaston, Cecil D.: An improved technique for perineal repair in the presence of rectal pathology. *Trans. Am. Proc. Soc.*, XXXIII, 159, 1932.

## Annual Abstracts of Protologic Literature

(May, 1934-May, 1935) By CLEMENT L. MARTIN, M.D., Chicago, Illinois

The complete bibliography from which these Abstracts were made will be published in full in the *Transactions of the American Proctologic Society*, 1935.

### AMEBIASIS

The occurrence of the disease in Chicago in 1933 caused chiefly perhaps by contaminated hotel water supply, resulting from leaky valves or cross-connections in old plumbing, served to fix the attention of the profession throughout the country on this disease. It is now rather generally taken into account when diarrhea is a symptom. Many atypical cases and a number of very acute infestations are reported. (See Brown, Simpson, and others).

Fresh stool examinations in clinical laboratories are becoming more reliable due to better training of the personnel in parasitology. Stool cultures are being used more in Chicago. Some authorities think no suspected stool should be considered ameba-free without a negative culture. The complement fixation tests have not had a wide acceptance as yet. Water transmission of the disease was again demonstrated by a number of infestations following the Stock Yards fire in Chicago in 1934, during which the water supply became contaminated.

Spector, Kaplan, et al, conclude from their work that contamination by carriers of *Entamoeba histolytica* under the ordinary conditions of food handling occur, if at all, quite rarely.

Arnold cites authorities for the belief that there are lumen dwelling *Entamoeba histolytica* which may invade the mucosa only when the susceptibility of the host changes. His own work demonstrated that the permeability of intestinal mucosa was affected by unfavorable changes in animal environment. Hot weather may be a factor in causing active infestation when amebiasis is present in the bowel.

It has long been known that diet has an influence in the disease, especially a restricted diet with relatively high carbohydrate ingestion. Faust and Kagg have shown experimentally that raw liver, liver extract, and cod liver oil caused recovery or improvement; dessicated hog stomach and canned salmon caused rapid and severe aggravation of the disease.

The articles of the speakers at the A.M.A. symposium on Amebiasis at Cleveland: Craig, Simon, Magath, Reed, Meloney, K. Lynch, and McCoy and Chesley, cannot be summarized. They present in excellent form current knowledge of the subject and repay reading. This is equally true of Craig's paper in the first issue of the American Journal of Digestive Diseases and Nutrition.

Diagnosis (See 1933 "Review").



The advantage of proctoscopic examination and of obtaining material from rectal ulcers is becoming better known and appreciated. *Soper* has emphasized this repeatedly. Several authors direct attention to this in the last year. *Melcney's* description of the colon lesions is what we ordinarily see, however, the diffuse granular appearance of the mucosa is not common, in my experience.

*Magath* relies on the direct smear for determining the presence of *Entamoeba histolytica*, stained with iodine or eosin in some cases for amoeba identification; 3 fresh stools are examined, ordinarily.

Therapy (See 1933 "Review").

Emetine retains its place for the control of the diarrhea and acute phase of the disease, and for hepatitis; the organic arsenicals or oxyquinoline derivatives are the effective amebicides, the latter especially are given with many variations of detail.

*Craig* advocates emetine hydrochloride and chiniofon (anayodin, yatren), 3 or 4, 0.25 G pills of the latter are given 3 times a day for 8 to 10 days. He treats the case with severe diarrhea by subcutaneous injections of 0.065 (1 gr.) of emetine hydrochloride daily for a period not to exceed 12 days. *Anderson* and *Reed* have used carbarsone rectally to control the severe diarrhea in acute cases. *P.*

*W. Brown* continues to obtain good results with emetine 3 to 4 grains for 2 days, giving at the same time treparsol 0.25 Gm.t.i.d., but continuing for a total period of 4 to 5 days. Intravenous arsphenamine is regarded by many as an inconvenient, expensive, and uncertain measure.

*Reed* advocates emetine hydrochloride, 1 gr. daily hypodermically (never intravenously) for 6 days. At the most these six doses may be followed by six of ½ gr. each. The total must never exceed 10 mg. per kilogram of body weight, or (0.65 Gm.) 10 grains for a man of average weight. Other forms of emetine and especially ipecac are not advised. He recommends carbarsone and vioform: carbarsone 0.25 Gm. in gelatine capsules, 2 or 3 times a day to a total of 20 doses or vioform in gelatine capsules 0.5 Gm. twice daily for 10 days. Ten day to two week intervals between the first and second course are usual.

Having been thus definite, *Smithies'* warning on the danger of standardizing treatment in this disease is worthy of comment. One can no more safely follow fixed dosage in this than in any other disorder. Kidney and liver function must be watched when using arsenicals, emetine's effect on heart muscle should be borne in mind.

*Reed's* subdivision of these cases into groups, makes his article on treatment particularly worth while.

## SECTION VIII—Editorial

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastroenterological Association is in no way responsible for editorial expressions.

### THE JOURNAL'S SECOND BIRTHDAY

THE Editors and the Council have enjoyed watching the substantial growth of this Journal during the two years since its inception.

An ideal toward which effort now is being exerted is greater *brevis* in the articles which we shall publish. We seek the cooperation of contributors. Eventually, the need for brevity must become appreciated by our profession, otherwise, medical literature is destined to become forbiddingly prolix and its substance attenuated. Genuinely new material is rare; it is best exhibited and understood when not lost in language.

Beginning with Volume 3 (March, 1936), there will be but a few minor changes in the Journal's format. Such will conform with certain suggestions sent to the Supervising Editor by interested readers.

One outstanding explanation for the Journal's unusual progress lies in the remarkable interest shown by its audience throughout the United States, Canada, and Europe. Many readers have manifested an actual, individual concern with several aspects of this magazine, a feature as unusual as it is pleasing.

From our advertisers, we are gratified to learn that their use of our pages actually has brought results, in even these days of economic uncertainty. No doubt the main reason for this happy circumstance, rests upon the plain fact that the readers of this periodical constitute a select and understanding professional group; they are "key-men" whose opinions and purchases influence others.

It is our hope that readers will continue to consider this Journal as their's, in a very real sense and to a large degree. Suggestions for its improvement not only are welcomed but urgently are solicited.

It is with keen appreciation of the *entente cordiale* which exists between readers and Editorial Staff that the Journal will present Volume three.

Beaumont S. Cornell, Supervising Editor.

### REGARDING THE "HOUSE" PAGE AND CERTAIN EDITORIAL PROBLEMS

PRACTICALLY all publications set apart a page to give information about themselves and better to guide prospective contributors.

These "House," "business" or "literary" pages often are unread, partly because custom may place them in obscure sections of magazines but, more especially because readers or contributors feel that "House" pages have no scientific value, hence are none of their concern. Such attitude is unwarranted.

This Journal's "House" page always has been—and still is—at the front of the magazine and behind the first non-cover advertisement page. It is recommended that readers, contributors and business people read the "House" page, at least once; it carries much information with regards the policies and the administration of this Journal. Let us emphasize certain facts.

When we print that this magazine is "The Only Monthly Periodical in Its Special Field on the Western Hemisphere," we are not boasting; neither are we attempting to rival or to cover so much territory as does the *Chicago Tribune*, with its inclusive slogan, "The World's Greatest Newspaper!" We state the envied position of the Journal because it is a fact and because that fact emphasizes the international opportunity open to contributors. That this Journal eagerly is looked for in countries of the Western Hemisphere,

other than the United States, is evidenced by the abundant correspondence, requests for reprints, books, abstracts and the like which reach both its business and its editorial offices. That the advertiser finds this Western Hemisphere coverage of significance is proved by the number of direct enquiries which reach him, particularly from Latin America. One South American technical magazine on two occasions has sought permission to re-print, *in toto*, articles which the Journal has carried.

"The Only Monthly Periodical in Its Special Field on the Western Hemisphere" is not a boastful slogan; it is a *fact*. Such being so, Editors and Publishers alike recognize that this unique status imposes upon them a large measure of responsibility. On them, it is incumbent, that this Journal carry to its readers only such material as represents the most reliable and advanced investigative and clinical effort. Further, that this periodical bend every energy towards *promptly* printing data in a form which is easy to read and which is supplemented by the most skilled exhibition of tables, charts and photographs. In these respects, while the goal set not yet has been reached, voluntarily many readers, have stated that the close collaboration existing between the Supervising Editor, Dr. Cornell, and the printers, has resulted in the production of one of the most technically attractive medical magazines extant.

The issuance, monthly, of any journal throws a tremendous routine burden upon those who work to a time-schedule. "Heavy" cerebral action not necessarily is demanded—even though it may be welcomed). The purely physical maneuvers required are a real task for the small group entrusted with the duties of "pushing things through." It is in respect these routine duties that perusal of the "House" page vastly would lighten the task of the "Office"—of men who work earnestly and willingly without thought of financial reward. We list a few of the ways by which the "Office" could be helped if readers, contributors or business fold carefully would scrutinize the "House" page.

(a) Dozens of letters asking about subscription or single copy rates would not demand the time and the expense of answering.

(b) Manuscripts would be prepared, *before submission*, in a fashion which greatly would facilitate their being read; more quickly then, would Authors learn of acceptances, revisions, rejections.

Graphs, charts, tables, photographs properly would be designated and made understandable without lengthy correspondence and thus not lost with regards "tops," "bottoms," "legends," "right" or "left," or even with regards manuscripts to which they belong. A weary, perplexed Editor but proves he is human when he casts a stoney eye on a sloppily-typed, miserably organized manuscript or spends half an evening endeavoring to hitch a group of blurry pictures, arm-long tables or monotonous, wordy "case histories" to a lot of typed sheets which are not even numbered!

(c) "References" in keeping with the subject matter of a manuscript are desirable. All too often, Authors submit "bibliographies" of encyclopoedic length, with incorrectly spelled names of workers or journals, errors as to subject, volume, pages, etc. Oft, indeed, it is evident at a glance, that such bibliographies are not germane to the text, are not known inti-

mately to the essayists and appear only for the purpose of impressing the general reader—which, of course, they don't, inasmuch as only readers interested in the topic being discussed give attention to bibliographies. When such special readers do so, very quickly doubt is cast upon the subject presented, when it is noted that the reference lists palpably are inaccurate or not specifically called for. Being generous with his bibliography not always is an indication of a writer's language-knowledge, broad understanding, reading or of general erudition. Not uncommonly, a vast bibliography is a tail which wags a feeble scientific dog. Besides, it's a costly affair to "set up" such an eye-laming punishment to Editors and proof-readers.

(d) Authors who speculate respecting what has become of their manuscripts would do well to recall whether or not the contributions were sent to the *Editor* or to the *Business Office*; whether they traveled at *first class* rates, and in *sealed* containers which carried Authors' return *addresses*; whether return postage was enclosed; whether illustrations were protected against the quite good-natured, tho destructive activities of the mail-handlers.

(e) Good sportsmanship is an outstanding American characteristic. Occasionally poor sportsmanship crops up, even among physicians and scientists. Its most common evidence lies in failing to give credit to men who have done original or meritorious work on subjects being discussed; in quoting *partial* paragraphs which do not carry the entire sense of another's observations; in casting doubt upon men or institutions and their efforts, should those men be not "Olympians" or their work-shops be rivals; in making excerpts from important papers and then *forgetting*. (!) properly to include those small, but all-important, quotation marks; in appropriating whole blocks of references or—this, we are happy to admit is rare—wilfully plagiarizing entire articles (even to the degree of not crediting illustrations!) which previously have been published, perhaps in journals (often foreign) or Transactions not readily accessible to the average reader. There is nothing more reprehensible or contemptible than the theft of another's brain-children! Manuscripts sent to this Journal are assumed to be *original* efforts, not rehashes, slickly disguised summaries or outright stealings. While, in such circumstances, Editors may be deceived, readers are not. Within a few days following the printing of these spurious essays, critical and condemning communications pour into the Journal's office.

Means whereby these imposters, who chance to have degrees in medicine, could be disciplined—even to their expulsion from reputable organizations of physicians—imperatively would seem to be called for. Their crimes are not just thoughtlessness or carelessness. Preparation of medical essays requires too much time and effort to credit such excuses. Those "Authors" deliberately steal men's brain work and present the results for personal advertising purposes. When commercial organizations throughout the land punish and ostracize dishonest advertisers, it is high time that the medical clan purge itself of "research" fakers and copyists. At any rate, it might curb these glib arm-chair and library "investigators"—clinical or laboratory—to know that in any Editorial Office deserving that name, they are recognized and listed.

(f) Orders for reprints are purely business transactions. They should be sent to the *Publication Office* when Authors return corrected proofs to the publishers. Reprint orders sent to the Editor mean only delay, increased expense of operating that office or in the orders' being mislaid or lost. The manufacture of Authors' reprints represents a courtesy to contributors. Rarely do publishers "break even" on reprints. If they do not, then the expense wholly is borne by the publishers. It is but fair that Authors recognize this fact and promptly pay for their reprints. In these days of economic stress, few publishers can afford to pay for the reprints of others' articles—i.e.—actually to pay for the privilege of printing Authors' essays and, also for their publicity-programs—for, often that is just the use to which huge numbers of reprints are put.

(g) Books for purposes of review are an Editorial responsibility; the Business Office has no concern with such matters. Publishers and Editors find it expensive to ship the many weighty volumes of medical-today hither and thither, in order that they may reach their proper destinations. This Journal's reviews are made by competent men whether they be or be not members of its Editorial Council. Further, it is our policy to have reviewers actually *read* the new books and thus then to see to it that their comments sufficiently are inclusive to give readers bases upon which they may determine whether or not the books will prove valued additions to professional libraries. That the Journal's reviews are appreciated is evidenced by the many congratulatory letters received from publishers. Occasionally, a subscriber takes time off and expresses his approval of a recently printed, particularly brilliant review. Finally, reviews are printed without censorship by the Business Office.

(h) As this Journal approaches the issuance of "Volume 3," it is not inappropriate again to mention that its policy does not permit the whole-sale piratical plundering of its pages by the lay or the medical-business-man publisher of those "sent free," bound collections of advertisements which call themselves "magazines." Contributors should appreciate the en-

deavors put forth by this Journal that they be protected from these shameless parasites who, at times, hiding behind the names of publicity seeking physician—"editors," publish scrambled, often ridiculous and misleading "abstracts" of articles which have appeared in reputable periodicals. This Journal's entire contents are copy-righted. Contributors are protected from "scissors-editors" and "immature publicist" wise-crackers' by our constant, monthly survey of the "gratis" magazines. We believe that the really earnest clinicians and investigators appreciate our efforts. It is of interest to observe that the contributor who occasionally sends a note stating that he has given permission to the publishers of the "Current Economist," and its like, to abstract his essay already printed in this Journal is one of those who has failed to read our "House" page; if he has read it and still wishes to split his modicum of sciences or medicine with the "ad" sheets dressed up to represent a magazine, then it is not difficult to judge why he publishes. Needless to say, his next contribution finds no space available in the Journal.

(i) Not being sufficiently clever to enjoy cards, we have but scant knowledge of the various possible combinations which may make a game, and less, perhaps, of the lingo of the card-player. However, we believe that out of the latter there has come the word "Kibitzer." Our understanding of this hybrid word is that it signifies one who does not play but who ever is ready to look over others' "hands" and offer advice. This Journal seems greatly to have stimulated the growth of the "Kibitzer" clan. For a periodical to be talked about is considered in some quarters, a half-won battle. During the coming year we hope to translate many "Kibitzers" into "Subscribers." If those who now faithfully remit annually will be rather selfish of their Journals and not pass them out freely to the "Kibitzers" our task will be an easy one. We are so hardened that we venture to hope that, in respect the "Kibitzers" and *your* Journal, you will make "Old Scrooge" look like a philanthropist.

Frank Smithies, M.D., Editor-in-Chief.

## SECTION IX—Book Reviews

(This section is open to contributions from any medical reader, whether or not a member of the Editorial Council).

*Aids in Diminishing Operative Risk. Preparation. Anesthesia. Post-operative Course. Transfusions. Infections (Pour Diminuer Le Risque Operatoire. Preparation. Anesthésie. Suites. Transfusions. Infections),* by Depuy de Frenelle. 91 plates, with an alphabetic index of Authors, an index of the subject matters by chapter, and a table of plates. (2nd Edition) Librairie Maloine, Paris, France.

THE work is divided into five parts. The first explains clearly the investigation for determining the resistance of the patient to operation (the ability of the patient to withstand operation), which is established after an examination of the urine, of renal function, of the blood, and after determination of the blood pressure, both arterial and venous.

The second part deals with the preparation of the patient for operation; pre-operative diet is mentioned with details for the different types of disease, uremia, diabetes, hypotension, etc.

In the third part the Author considers the preventive treatment of post-operative complications.

*Infection.* Preparation of an infected patient for operation. Prophylaxis and treatment of the infection by vaccine and antiviral therapy. Serotherapy, irrigation and drainage, and chemo-therapy.

*Pulmonary complications.* Phlebitis and embolism. The ideal preventive for the last two named would be, according to the Author, rest in bed with active movements and operative gymnastics.

Prophylaxis of occlusion, of tetanus.

In the fourth part, the Author, with the collaboration of Luquet and Moons (of Anvers), gives a detailed description of the different methods of anesthesia. "Anesthesia is that stage of the operative act which still remains the furthest from perfection. It is the weak point of surgery."

The different modes of anesthesia, by inhalation, are reviewed and details of their technique given. The advantages and the inconveniences of each one are specified. Spinal anesthesia, epidural and para-vertebral anesthesia, transabdominal anaesthesia of the splanchnics, regional anaesthesia, local anaesthesia with novocaine, and anaesthesia by injection are all dealt with.

In the fifth part, the Author studies the methods to be taken for diminishing the risk of operative shock and hemorrhage, the use of different serums, their indication, their value, and the technique employed in their use.

Blood transfusion is studied at length. Transfusion of whole blood, of blood treated with glucose, of citrated blood, with or without the addition of either salt or glucose are all considered. The indications for transfusion, the different techniques, and the dangers and accidents are clearly explained.

The study of this volume is highly recommended to all surgeons who are anxious to diminish operative risks by employing to this end all of the means, pre and post-operative, at their disposal. The reading is agreeable and easy, the text clear and precise, the rules and essential remarks are well underlined.

Pierre Smith and Thomas Farmer, Montreal.

*Dietetics for the Clinician: Second Edition.* By Milton Arlander Bridges. Published by Lea & Febiger, Philadelphia, Pennsylvania, 1935, 970 pages.

THE general plan of the second edition of Bridge's book, "Dietetics for the Clinician," has not been changed from that of the first edition. The principal changes that bring the book up to date are: Revision

of the sections on Physiology and Chemistry of Digestion, Vitamin Factors in Diet, Selection and Preparation of Foods, Allergic Diseases, Dentistry, Tuberculosis, and Pediatrics. These subjects have been rewritten and amplified in approval of the more recent investigative work.

In the *Part I*, the Author discusses briefly but clearly the Mechanics, Physiology and Chemistry of Digestion. Only the practical essentials of the metabolism of food have been explained. A section is devoted to the Selection and Preparation of Foods and to various recipes.

*Part II* discusses the Dietetic Management of Disease of Adults, and *Part III* is devoted to Pediatrics. Diseases and their Diets are discussed from the physiological and pathological needs of the patient suffering from the disease. Many sample menus for the various diets are presented and detailed lists of those foods to be used in limited amounts, or omitted entirely from the diets, are given. Throughout the book there are many practical medical and culinary suggestions of value.

The section devoted to miscellaneous subjects on dietetics, Food Adjuncts, Special Methods of Feeding and Practical recipes, is a very useful portion of the book.

Other features that enhance the value of this work are, The Food Table, in the appendix, and the Definitions, of, and a modern table analyzing the various alcoholic beverages.

This book offers to the physician, dietitian, and nurse a useful and authoritative presentation of the subject of Diet and Nutrition in a non-technical style, practical and physiologically sound.

Clifford J. Barborka, Chicago.

## SECTION X—After "Hours"

JOHANN GREGOR MENDEL\*

By

J. DUFFY HANCOCK, B.S., M.D., F.A.C.S.  
LOUISVILLE, KENTUCKY

### INTRODUCTION

MANY men achieve desired and lasting prominence while they are still alive to enjoy it; others, less deserving, may have that same pleasure if they are fortunate enough to die at the right time before the shallowness of their pretensions is realized; some few leave accomplishments that are gradually appreciated

as time "separates the wheat from the chaff"; but rarely does a man die in obscurity and yet, in the very next generation, have his name elevated among the immortals and his fame constantly increased. Such a man was Johann Gregor Mendel, promulgator of the Mendelian Law of Inheritance and Abbott of the Augustinian Monastery of St. Thomas at Brunn.

My school-day interest in this man was revived and intensified by reading Hugo Iltis' "Life of Mendel" to

\*Read before the Innominate Society, Louisville, Kentucky, November 15, 1934.  
Submitted October 23, 1935.

which I am indebted for much of the biographical data that follows.

### THE YOUTH AND STUDENT

A hundred years bring many changes—especially in the map of Europe. One reads that Mendel was born in Heinzendorf bei Odrau in Austrian Silesia. To find his birthplace now one must look in the north-eastern corner of Moravia in that part of Czechoslovakia at whose border the boundaries of Germany and Poland meet.

On July 20, 1822, when Johann Mendel was born, the villagers little realized the contribution their new neighbor would make to that age of scientific progress guided by Asa Gray in America. Pasteur in France, Lister in Scotland, Darwin in England. Helmholtz and Kach in Germany and Mendel in Austria—a partial list of the outstanding lights of a new scientific age.

Mendel was the second of three children; the two others were girls. He was christened simply "Johann"—the additional name of "Gregor" being taken when he became a member of the Augustinian order. His parents were "free-men" but peasants, his father being required to work three days of each week for the neighboring Noble. From early childhood, both on the farm and at school, he was interested in natural science and improved methods of cultivation.

After preliminary education in the local village school, Mendel matriculated, at the age of 11, into a higher school at Leipnik and later was admitted to the Troppeau High School. There the headmaster was Pater Ferdinand Schaumann, an Augustinian monk from the monastery at Altbrunn. Due to lack of finances it was with great difficulty that Mendel was able to complete the course. He had to work his way through school and knew what it was to be hungry.

His eagerness for more knowledge led him to apply, unsuccessfully, for a position as private tutor in Olmutz where he hoped to attend the Philosophical Institute. That he was finally able to enter was due to the fact that his father, now ailing, deeded the farm to a son-in-law with a proviso that some contribution was to be made towards Mendel's maintenance while a student. Even that was insufficient, and worry over the situation resulted in a protracted sick spell for Mendel. At this time his younger sister, Theresia, came to his aid by renouncing her share of the family estate and thus enabled him to resume and complete his studies at the Philosophical Institute.

Shortly after graduation, he had an opportunity to enter the Augustinian order. While monastic life had a definite appeal, his private circumstances (financial) evidently played some part in his choice of professions. At any rate, on October 9, 1843, he was admitted as a novice at the Koninginkloster.

### THE TEACHER AND PRIEST

Fortunately for Mendel, the Monastery of St. Thomas (Koninginkloster) at Brunn (Altbrunn) was one of the chief centers of the spiritual and intellectual life of the country. Almost immediately Mendel began to devote his spare time to the study of the small botanical and mineralogical collection at the monastery. At the end of his novitiate, he began the four year theological course embracing ecclesiastical history, archeology, and law, dogmatics, moral theology, pastoral divinity, methodology of elementary school education, Hebrew, Greek, Syriac, and Arabic

languages, agriculture, and other subjects. His work, diligence and behavior always were excellent and by special dispensation he was ordained a priest at the age of 25—before he was quite through with his studies. This dispensation was granted since there was an unusual shortage of priests at the monastery at that time.

For a few months after his graduation Mendel was an assistant parish priest. This work, however, was distasteful to him because of his timid, sensitive nature, which made visits to those ill and in pain an ordeal which seemed to upset him nervously. For that reason he welcomed an appointment to teach in the high school at Znaim. Since he had not attended a university or passed a teacher's examination, his position was that of a deputy or "supply" teacher. In 1850, without benefit of university training, he failed the examination in Vienna for a teacher's license. In 1851 he substituted for a few months at the Brunn Technical School. Upon his release from this position he attended the Vienna University from 1851 to 1853, studying physics, chemistry, botany, zoology, mathematics, and the practical use of the microscope. While a university student, he tried his luck in a lottery but the calculus of probabilities failed him.

In 1854 Mendel was appointed "supply" teacher at the Brunn Modern School and taught there for the fourteen years until he was elected abbot. As a teacher of zoology, botany, and physics he was not only competent but also gentle, kind and cordial. He seldom allowed a student to fail—coaching those who needed it without asking any special fee. He was fond of all animals except snakes, which he feared. Among his pets were a fox, hedgehog, birds and mice. In speaking of his breeding experiments, he used plain terms to describe matters of sex and when once some of the pupils tittered said, "Don't be stupid! These are natural things"—a rather liberal attitude at that time. In 1856, again he tried the teacher's examination at Vienna. Whether he failed or retired from the examination, he was, at any rate, unsuccessful and continued from then on as a "supply" teacher although all his colleagues were fully accredited.

While there are no hints that he was ever insubordinate, dissatisfied or negligent in his religious duties, he was not prominent as a priest. His chief interests, evidently, were scientific. He enjoyed teaching and, during those happy days, worked out his contribution to the scientific world. However, much of his success was probably made easier by the freedom from financial worry and the time for contemplation afforded by his monastic life.

### THE SCIENTIST AND DISCOVERER

From early childhood Mendel had been interested in gardening. Later, as priest and teacher, he began some haphazard work in hybridization and had even for a while bred mice in his room. His main interests, however, were always botanical rather than zoological, and if he kept any records of his experiments with mice they have been lost.

Although he cared nothing for fiction, Mendel read extensively in many fields of science; in the monastery library there are still many of his books with notations and comments in his handwriting. It is foolish to say that Mendel had no fore-runners, for he did, as have nearly all discoverers. Although their ground



work was based on insecure foundations, probably they influenced and certainly inspired him in his research. References in his writings show both knowledge and acknowledgement of the work of others but it conclusively can be demonstrated that he was the first to carry out the definitely planned experiments and to deduce scientifically those facts which are basis of his law.

For several years before 1856, Mendel had made rather extensive observations on hybrids of flowers as well as of the common, edible, garden pea; it was probably chance discoveries which, in that year (when he was but 34), led him to begin his careful experimentation. This continued for about seven years; two years after that, in February, 1865, his history-making paper, "Experiments in Plant-Hybridization," was presented before the Brunn Society for the Study of Natural Science.

In his attempt to study the law of hybrids, Mendel's methods differed from those of his predecessors in several ways. Instead of selecting species or varieties that differed in many qualities he chose those differing only in respect to one or a few characters. In addition to observing only the various characters presented by the hybrids, as others had done, he paid especial attention to the numerical ratios presented by the hybrids. This inclusion of *mathematics* with botany was an entirely new departure. His other original experimental procedure was the individualization of plants and their seeds. He regulated the planting and fertilization of each plant and studied each generation of hybrids separately rather than considering the whole of the offspring as a great chaos.

After careful consideration of the pea, Mendel decided to ignore characters that were rather quantitative in nature and to concentrate on those which were qualitative and paired. The seven contrasting pairs of characters selected were: 1, the shape of the pea (round or wrinkled); 2, the difference in the color of the cotyledons (yellow or green); 3, the tint of the seed coat (white or else gray, grayish brown, or huff with violet spots); 4, the difference in the shape of the ripe pods (simply curved or deeply constricted between the seeds); 5, the difference in tint of the unripe pods (green or yellow); 6, the difference in the position of the flowers (axial or terminal); and 7, the difference in the stature of the plants (tall or dwarf). Consideration of these factors by use of the methods just described gave Mendel the information upon which his deductions were based. An eighth character, the blooming season, later was studied and fairly well elaborated, but this was after the publication of his important monograph. It must be remembered, too, that these pairs of divergent qualities may be intermingled; for example, to use a very elementary illustration, tall or dwarf plants may have green or yellow pods, etc.

A detailed description of Mendel's experiments probably would be boresome to the reader—a complete analysis and explanation difficult for me. Therefore, let us consider only a few simple findings. If a tall race of peas is crossed with a short race, all the progeny in the *first* filial generation are tall. This is because tallness is "dominant" to shortness which is "recessive." When these tall hybrids are self-fertilized, as is normal with the pea, their offspring, the *second* filial generation, will be partly tall and partly short, in

the proportion of three tall and one short. The quality of shortness, it is apparent then, was not lost or blended but was only suppressed for the time being and the offspring of this short plant, self-fertilized, will all be short. The offspring of the tall plants will, however, vary. One tall plant will breed true as did the short one and all its offspring will be tall. The offspring of the other two tall plants will be partly tall and partly short in the proportion of three tall to one short. This illustrates Mendel's first fundamental, that *segregation* rather than *blending* occurs when hybrids are formed.

The other law, that there is an independent assortment of different pairs of qualities, can be shown in its simplest form when individuals with two pairs of contrasted characters, each exhibiting complete "dominance," are crossed, all types will be produced in the *second* filial generation. These represent the original distribution of the characters and the two possible recombinations between them. Since each type, considered separately, will appear in a 3:1 ratio in this *second* filial generation, the four will be brought together in a combination of two such ratios: that is, 9:3:3:1. Of these sixteen types, nine will contain one member of each dominant pair, three will be without one dominant type, and three without the other, while one will have all its factors "recessive"; and further, of these sixteen plants, one-fourth (composed of one member of each of the four types) will breed true. Contrasting this dihybrid with the previously mentioned monohybrid (tall and short only), we find of the sixteen combinations only nine distinct forms as compared with four combinations with three forms. Mendel showed that, in more complicated hybrids, the number of combinations would always be evidenced in a smaller number of forms which could be expressed as 3 to the *n*th power, *n* being the number of contrasting characters. We shall not consider these further than to say that Mendel, with infinite patience, was able by repeated crossings to produce all the possible combinations of the seven paired and contrasted characters previously mentioned.

$$\begin{array}{rcl}
 9 (4AaBb + 2AaB + 2ABb + AB) & = & 4AB \\
 3 (2AaB + Ab) & = & 2A \\
 3 (2ABb + aB) & = & 2B \\
 1 (ab) & = & 1ab \\
 & & 9 \\
 3 (A + 2Aa) & = & 2A \\
 3 (A + 2Aa) & = & 1a \\
 & & 3
 \end{array}$$

The "Mendelian Law" is, therefore, based upon *two fundamentals*. These are *first*, the *segregation* of contrasted unit-characters when pure-bred individuals are crossed, and *secondly*, the *independent assortment* that occurs when two or more pairs of contrasted characters are brought into the "cross." Since Mendel worked before the development of cytology, of course, he did not realize that the nucleus was the responsible part of the cell and that these unit-characters were present in the chromosomes. This latter amplification has somewhat modified the second fundamental (that of independent assortment) and furnishes the additional factor of *linkage* which, showing the numerous characters that must often be present in a single chromosome, explains apparent discrepancies that occur in some instances of "crossing" when multiple contrasted characters are present. Sex-linkage, cross-



ing-over, and mutation are other additional factors that have been incorporated in the Mendelian Law to make it more generally applicable.

The only other plant that Mendel wrote much about was the hawkweed. Experiments with this were done at the request of Nageli, a prominent German botanist. Only in their correspondence do we find references to numerous other plants studied by Mendel. A partial list includes columbine, snapdragon, plum, pear, bean, flax and nasturtium.

Before dismissing the scientific work of Mendel, mention should be made of his efforts as gardener, bee-keeper and meteorologist. As a gardener, his principal interests were with fruits and wild flowers. He secured seeds from many, widely separated parts of Europe and, today, in the monastery garden are Florentine grape vines and many fine fruit trees marked with a leaden seal bearing the initials "G.M." The old gardener there, who died a few years ago, is authority for the statement that Mendel affected five to six hundred crossings of fruit trees, raised their seedlings and grafted some of them on older trees.

Mendel's bee-hives are still intact, as are his original sketches for their construction. His experiments here were not limited to hybridization but included study for determinization of the best type of food, protection of the hives from mildew and control of disease among the bees. The only account I could find of any display of humor on Mendel's part was in connection with his observations on bees. The incident is so quaintly expressed by the victim, Pater Clemens, that I shall quote him verbatim: "One day towards the end of winter (it was in early March, and the ground was still under snow, but the sun was shining already with the warmth of early spring) we came to the bee-hives and watched the bees which the sun was already attracting forth from the hives. With a roughish smile, Prelate Mendel told me, then a youthful priest, to lay my black biretta on the white snow in front of the hives. He looked on with a grin when all the bees promptly settled on this attractive black patch, which very soon was yellow instead of black, for the bees used it as a site on which to void that which, for reasons of cleanliness, they had refrained from voiding in the hives during the winter."

One would think that these varied interests would have been sufficient for even so many-sided a man as was Mendel. However, he had time for meteorological studies. He was collaborator at Brunn for the Central and, later, for the Vienna Meteorological Institute. The barometer, maximum-and-minimum thermometer and rain gauge which he used were located each at a different part of the monastery grounds and, until less than a month before his death, he made thrice daily observations of each instrument. In addition to these regular tasks he made a study of sun-spots, of the level of the subsoil water and of the tornado which struck Brunn in 1870. These meteorological observations were the principal scientific attainments of his later years.

In the versatility of his interests, Mendel shows a trait so common to many men of eminence. The same is true in regard to the immense volume of work he managed to accomplish. Indeed, he well exemplified

the truth of the old adage that if one has a task to be done he should ask a busy man to do it.

### THE ABBOTT AND BISHOP

As an ordinary monk, Mendel had access to a very little garden on which to conduct epoch-making observations. He had hoped, however, when he was elected abbot, that, with the entire gardens, at his disposal he could do much more work than ever before. Unfortunately for science, the responsibilities of his new position kept pace with its honor and authority. After his election in 1868, experimentation became an increasingly unimportant part of his life—not that his interest lagged but his time was occupied by other duties. His selection as abbot, or more strictly speaking, prelate, of his local religious community was not a complete surprise to him as we find mention of its possibility in a letter to his brother-in-law several days before it occurred. While he may have regretted his promotion later when he realized that it meant virtually the end of his experimental work, Mendel appreciated at the time the honor of his new position. This position was more than that of an ordinary abbot in that the prelate of the Koninginkloster was mitred—that is he carried the rank and actual office of a bishop. It was indeed an achievement to bring satisfaction to the peasant-born youth. Some of his satisfaction is evident in a letter to the great Nageli who had sometimes been rather condescending in his scientific correspondence to the "supply" teacher. Mendel's elevated position, however, did not make him forget his early friends. Out of his own funds he educated the three sons of his sister Theresia who had sacrificed her dowry for him. Then, too, he financed the establishment of a much-needed fire brigade at his native Heinzendorf in recognition of which he was made an honorary member.

He travelled some, entertained as his position required, was a patron of music, became curator of the Moravian Institute for Deaf Mutes, served as chairman of the Moravian Mortgage Bank, took an active interest in numerous scientific societies, was made commander of the Order of Francis Joseph and was active politically as a member of the German-Liberal Constitutional Party. When we realize that most of the religious opposed him in this affiliation, it seems most distressing that this very party was responsible for the passage of the bill which caused him so much strife and bitterness.

This bill was one that required regular religious communities to pay special taxes to a religious fund which was used to aid Catholic worship and to pay parish priests. Mendel's fight was not against the Church but against the State. He opposed this tax on several grounds: it was a discriminatory tax on a special group, the Catholic Church was not a state church and to him it appeared unconstitutional for the state to tax for the benefit of a private organization; further he claimed that his particular monastery had some years previously been exempt from such legislation. Other monasteries joined in the fight but the bill was declared constitutional and they gradually acceded. Mendel, though, regarded the issue as a "struggle for the right" and resisted the enforcement of the bill as long as he lived, in spite of threats, offers of bribes and sequestration of monastery income. Shortly after his death, the monastery accepted the law and was refunded monies drawn in excess during

the period of sequestration. The fight made Mendel was quite bitter and his friends gradually lost patience with his persistency, or obstinacy as one may choose to call it. With this separation from intimates, Mendel found relaxation in chess, not only playing the game well but inventing many problems in it.

With advancing years the family tendency towards obesity became more apparent. Several years before his death, Mendel developed chronic kidney disease and later organic heart disease and general dropsy. His pulse was frequently around 120 but he refused to reduce to any great extent the 20 mild cigars he usually smoked during the course of a day. He contemplated death stoically as a natural necessity but he feared premature burial. Possibly because of that, he exacted a pledge from his physician nephew that an autopsy would be done. The end, hastened by uremia, occurred on January 6, 1884.

Mendel's death was universally mourned in his immediate locality. Governmental officials, Protestants, Jews, neighbors, religious brothers and many of the poor whom he had helped so kindly, gathered to pay their last respects to Johann Gregor Mendel, the abbott. Mendel, the scientist, was eulogised twenty-five years later when a memorial to the investigator was erected at Brunn.

#### APPLICATION AND POSSIBILITIES OF THE MENDELIAN LAW

Mendel's records of his researches remained lost for about 35 years. This seems surprising for, although the Brunn Society for the Study of Natural Science was purely a local one and its "Proceedings" an obscure publication, nevertheless its publication was exchanged for those of numerous other societies on the continent and Mendel's studies should have been noticed earlier. The year 1900 marks the rediscovery of the essay. Within a few weeks of each other, de Vries, Correna and Tschermak independently published papers confirming by experiments the substance of Mendel's conclusions. A new era opened but it had taken science 35 years to learn what Mendel had already proved, years that could have been used in advancing knowledge rather than in trying to catch up with the advance which Mendel had made.

In considering the *application and possibilities* of the "Mendelian Law," both the theoretical and practical aspects must be reviewed. From a theoretical standpoint its possible place in explaining the theory of evolution is most interesting. To understand this, we must orientate ourselves in regard to this theory and not confuse "Darwinism" with "Evolution." Darwin simply tried to explain evolution as the result of natural selection—the weeding out of the *unfit* through survival and dominance of the relatively *fit*. The weak point to this is, obviously, the infinite time that must be required for minute changes to accomplish this. de Vries' "theory of mutation" (a *departure from type* suddenly developed in a *single generation*, explainable by change in habit, environment or nutrition) seems more plausible but still not so convincing as Mendel's theory and proof which permit hereditary changes and yet in no way involve the idea of chance or innate change. While Mendel became familiar with all Darwinian literature after he had

begun his own experiments it is unfortunate that Darwin never heard of Mendel's work. According to Bateson, "had Mendel's work come into the hands of Darwin it is not too much to say that the history of the development of evolutionary philosophy would have been very different from that which we have witnessed."

Viewed from a *practical standpoint* untold benefits may be reaped by the application of the Mendelian Law. For instance, susceptibility and immunity of wheat to rust have been demonstrated to be a pair of Mendelian characters, of which susceptibility is "dominant." By cross-breeding susceptible plants with otherwise desirable qualities and immune plants with some undesirable qualities, a pure strain of immune plants with other desirable qualities has been produced experimentally. Similarly horns, a "dominant" character, have been crossed out of sheep with characteristics otherwise entirely desirable. In considering horses that are naturally pacers or trotters, it has been found that pacers are "recessive" to trotters. Numerous other instances might be noted and will undoubtedly be developed.

The most important of all fields applicable to the Mendelian Law is, of course, the human race. Students of eugenics and genetics barely have scratched the surface here. While much must be learned regarding unit characters as well as linkage it is likely that Mendelism is as certain as in the other instances quoted but, as has been said, it will be of little use so long as wisdom lags behind personal liberty. Claw-hand, color blindness, presenile cataract and mental deficiency are said to be unit characters. The great obstacle to the study of the human race is the slow reproduction of successive generations. Speculation of what the future will show offers a fascinating diversion.

#### CONCLUSIONS

In concluding this rather rambling consideration of Father Mendel and his work, it might be well to summarize our impressions of him as a man.

He was from sturdy farmer stock. Poverty was his lot from early boyhood. While he was endowed with an excellent intellect, he worked energetically all his life to develop it to the utmost. In his scientific investigations he was characterized by attention to the most minute details, his insistence upon facts, his simplicity of method and his separation of the scientific from religious factors. Absolute integrity is apparent in all aspects of his life—mental, moral, religious and scientific. Although of a most serious and rather bashful nature and, in his later years, rather embittered because of controversy with civil authorities over what he considered a matter of principle, Mendel was thoroughly human. His affection for his family, his gratitude to his sister who sacrificed her dowry for his education, his hopefulness with the lottery ticket, his belief in his own abilities, his satisfaction in his accomplishments, his liberal generosity and his personal interest in friends and kindred workers all were marks, not of an eccentric or cold recluse, but rather of a normal human being, the kind of a man who would be an inspiring teacher and delightful acquaintance.

As an organizer and executive Mendel would be a most welcome addition to any scientific or lay society today. Finally, he not only drafted the modest announcement of his death but also proved his ability as a prophet in regard to the resurrection of his works by his statement to his friend Niessl, "*Meine Zeit wird schon kommen.*" His time did soon come. In a niche beside Darwin, Mendel's renown is so secure that the

future can only enhance it, but through that fame will shine the man mourned by Pater Clemens as  
 "Gentle, free-handed, kindly to one and all,  
 Both brother and father to us brethern was he.  
 Flowers he loved, and as a defender of the law  
 he held out against injustice,  
 Whereby at length, worn out, he died from a  
 wound of the heart."

## REFERENCES

1. "Life of Mendel"—Hugo Ilits—W. W. Norton & Company, New York, 1932.
2. "Mendel's Principles of Heredity"—W. Bateson—Cambridge, 1909.
3. "Mendelism and Evolution"—E. B. Ford—The Dial Press, New York, 1931.
4. "The Human Side of Science"—Grove Wilson—Cosmopolitan Book Corporation, 1924.
5. "History of Medicine"—Fielding H. Garrison—W. B. Saunders Co., Philadelphia, 1917.
6. "General Biology"—James Francis Abbott—The Macmillan Company, New York, 1916.
7. "Biology"—Gary N. Calkins—Henry Holt & Co., New York, 1914.
8. "The Story of Modern Science"—(Volumes V and VI)—Henry Smith Williams—Funk & Wagnalls Co., New York, 1931.
9. "The Catholic Encyclopedia"—(Volume X)—Robert Appleton Co., Philadelphia, 1911.

## SECTION XI—Societies, Programs and Proceedings

### ANNUAL SESSION OF THE AMERICAN COLLEGE OF PHYSICIANS

**T**HE Twentieth Annual Session of the American College of Physicians will be held in Detroit with headquarters at the Book-Cadillac Hotel, March 2-6, 1936.

Dr. James Alex. Miller, of New York City, is President of the College, and has arranged a program of general scientific sessions of great interest to those engaged in the practice of Internal Medicine and associated specialties. Dr. Charles G. Jennings\*, of Detroit, is the General Chairman of the Session, and is in charge of the program of clinics and demonstrations in the hospitals, medical schools and other Detroit institutions.

Dr. James D. Bruce, Vice President, in Charge of University Relations, University of Michigan, is Vice

\*Sad to announce that Dr. Jennings has recently died.

Chairman of the Committee on Arrangements, and has in charge the preparation of an all-day program to be conducted at the University of Michigan on Wednesday, March 4.

Dr. Walter B. Cannon, Professor of Physiology at Harvard University Medical School, will deliver the annual Convocation Oration on "The Role of Emotion in Disease." Dr. Miller's presidential address will be on "The Changing Order in Medicine." About fifty eminent authorities will present papers at the general scientific sessions, while clinics and demonstrations will be conducted at the Harper, Receiving, Ford, Grace, Herman Kiefer and Children's Hospitals of Detroit.

E. R. Loveland, Executive Secretary.  
 Philadelphia, Pa.

## ABSTRACTS

ZINNINGER, M. M., M.D., AND MCCANDLESS, H. G., M.D.

*Drainage of the Common Bile Duct for Gall Stones.*  
 S. G. O., Vol. 59, No. 5, pp. 781-786, Nov., 1934.

This article is a review of the technique used at the Cincinnati General Hospital for drainage of the common bile duct and is based on a series of forty-two cases where drainage was instituted through the stump of the cystic duct and a series of twelve cases where drainage of the common duct was instituted through the duct itself.

In the forty-two cases where drainage of the common bile duct was instituted through the stump of the cystic duct, there was a post-operative mortality of 9.3%. The hospital morbidity averaged twenty-eight days. The tube was kept in place an average time of eleven days. It was felt that the total bile loss was less than where drainage was instituted through the common duct itself and that

there was less leakage of bile around the tube when placed through the stump of the cystic duct.

In twelve cases where drainage was instituted through the common duct itself, the mortality was 25%. The average hospital morbidity was forty-two days.

Because in this small series of cases the hospital morbidity was less, the operative mortality was lower and the total amount of bile drainage was less in the group of patients drained through the stump of the cystic duct, the Authors feel that this should be the method of choice for drainage. For adequate exploration of the common duct, a separate incision through the duct itself is usually necessary, but this should be closed primarily. The fact that it is necessary to remove the gall bladder before drainage can be instituted through the stump of the cystic duct, the Authors do not feel is a serious contraindication.

N. W. Swinton, Boston.

## SECTION XII—"The Clinic"

### Spontaneous Gastro-Colic Fistula

By

MILTON R. LOURIA, M.D.

and

EMIL ROTHSTEIN, M.D.\*

BROOKLYN, NEW YORK

**S**PONTANEOUS gastro-colic fistulae are seen as infrequent complications of primary neoplasms of the stomach or colon. Clinically, they are quite similar to gastro-jejuno-colic fistulae occurring as a complication of gastro-jejunostomy, and the two conditions usually are described in the literature under the single head of "gastro-colic fistula."

Gastro-colic fistula was first reported in 1755, by Haller (1). In 1900, Zweig (2) collected 70 cases from the literature; of these 11 had been diagnosed ante-mortem. Brinton (3) in a study of 505 cases of carcinoma of the stomach found that perforation was an infrequent occurrence, it being found in 17 patients (3.4%). Of these, 11, or 2% of the total, presented gastro-colic fistulae. White (4) states that 4% of gastric carcinomas perforate, Smithies (5), 2½-6%, while Friedenwald and Feldman (6) found perforation in only 3 cases out of a series of 1000. Voerhoeve (7) collected from the literature 105 cases of gastro-colic fistula (1912) and calculated its occurrence as 3.75% of gastric carcinomas. Verbrugge (8) in 1924 collected 216 cases of gastro-colic fistulae and gastro-jejuno-colic fistulae from the literature. Of these 95 followed posterior gastro-enterostomy and 121 were due to primary gastric or colonic malignancy. However the 70 cases prior to 1903 were all due to malignancy, while of those after that year only 30% were secondary to carcinoma. The reason for this is two-fold: increasing surgery is lessening the number of gastric and colonic tumors neglected to the point of rupture, and similarly, increasing surgery is adding to the number of gastro-enterostomies. Of Verbrugge's 21 cases from the Mayo Clinic,

2 were due to carcinoma of the colon, and the remaining 19 were secondary to posterior gastro-enterostomies. Balfour and Down (9) analyzed two groups of gastro-enterostomy cases, totalling 1244; 3% presented gastro-jejunal ulceration. The percentage of perforation (not stated) was high. Anterior gastro-enterostomies with jejunal ulcerations perforated into the anterior abdominal wall, usually with abscess formation. Posterior gastro-enterostomies tend to perforate into the mesocolon or into the colon.

#### CASE REPORT

A. L., Negro male, 55, laborer. Admitted to K. C. H. 3/15/35. Claimed perfect health until 1/15/35, when he developed severe pain in the lumbar region. This pain persisted intermittently for two weeks and then disappeared. It was associated with chills and chilly sensations. About six weeks prior to his admission to the hospital severe epigastric pain appeared. This symptom lasted until the time of his death. It was intermittent and cramp-like; it was intensified by food and partially relieved by vomiting. During this period, he became progressively weaker and lost from forty to fifty pounds. Vomiting occurred about one month before his admission to the hospital. It persisted intermittently throughout the course of his ailment. It was most marked after eating. The vomitus was described as foodstuff, and occasionally "foul brown matter." There was no gross blood noticed. During the entire illness, the patient was moderately constipated.

Upon examination, the patient was weak and emaciated, with marked *feet ex ora*. The essential findings were in the abdomen. There was marked epigastric tenderness extending into the left hypochondrium; slight bulging could be seen and felt to the left of the epigastrium but due to marked tenderness and rigidity accurate palpation was impossible. Nevertheless the presence of a mass was definitely diagnosed in this region. At this time the clinical diagnosis was carcinoma of the stomach. A few days after

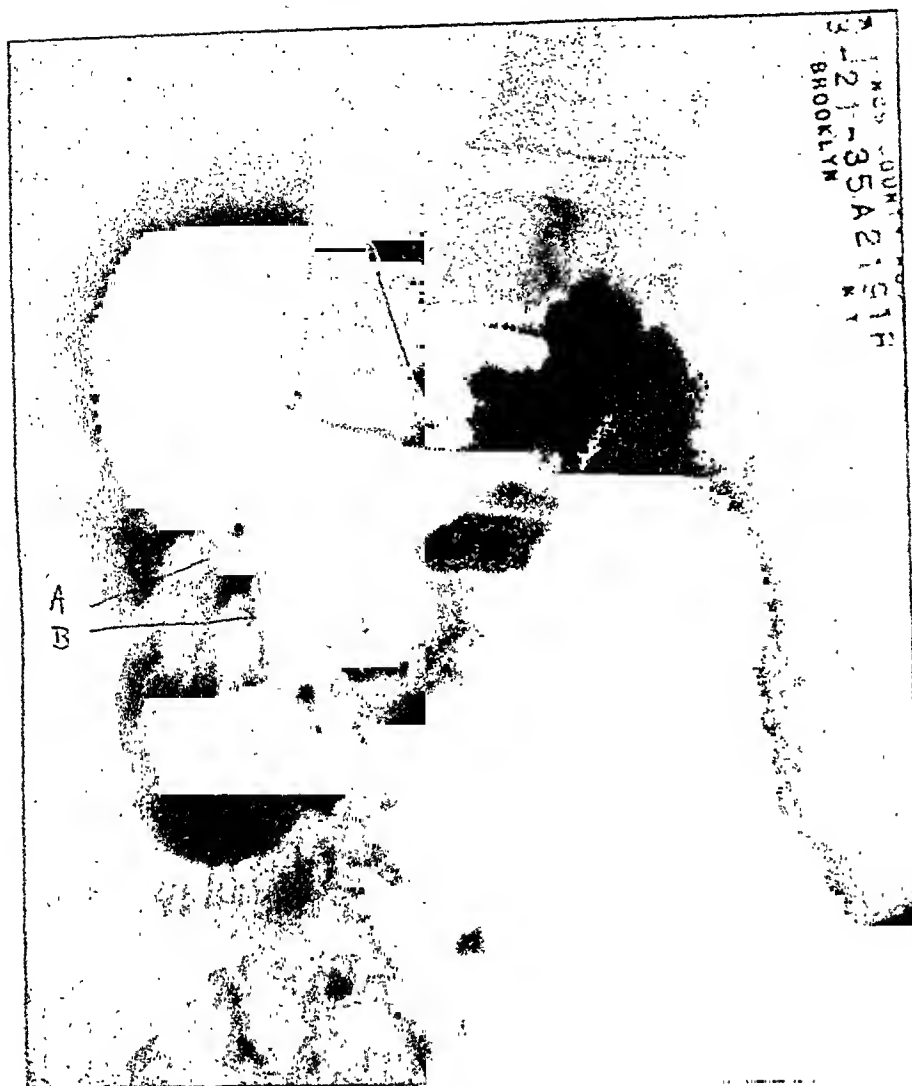
the admission note, a specimen of the vomitus was secured and examined. The following note was made: "The patient vomited profusely yesterday. The vomitus is apparently pure fecal matter. In the absence of signs of advanced intestinal obstruction this finding is pathognomonic of gastro-colic fistula, probably due to a ruptured carcinoma of the stomach." A few days later an attempt was made to confirm this impression by the dye test. The patient was given two capsules of methylene blue by mouth. Enemata given one and three hours afterwards, however, revealed no discoloration of the stools.

Laboratory data revealed the following: Urine—Neg. Stool—Positive for occult blood. Blood—Wassermann neg. Red count—3,000,000; Hbg. 65%; White count—11,000; Polys 81%. X-ray studies—Chest negative. Roentgen study: Fluoroscopy could not be performed due to the weakened condition of the patient. Similarly, in order to spare him several trips to the X-ray department (and before the clinical diagnosis of gastro-colic fistula was entertained) barium was given to him in bed and then in the X-ray department six hours later. Thus the presence of barium in the colon did not necessarily indicate any communication between the colon and the stomach. There was a constant filling defect in the pyloric portion of the stomach. The stomach plates, reviewed post-mortem, showed a large out-bulging deformity in the region of the greater curvature which corresponds with the ulcer and fistula found at necropsy. The clinical course was rapidly downhill with *crisis* two weeks after admission.

The autopsy protocol revealed: 1. Adenocarcinoma of the stomach with gastro-colic fistula. 2. Acute generalized purulent peritonitis. 3. Chronic adhesive pericarditis. 4. Chronic adhesive pleurisy. 5. Old healed fibrotic pulmonary tuberculosis. "There is an acute purulent peritonitis present involving all loops and surfaces of the visceral and parietal peritoneum. A large mass is found in the epigastrium, consisting of the stomach, transverse colon, and the right half of the pancreas. This mass is densely adherent to the gall bladder and the mesen-

\*Associate Attending Physician and Junior Visiting Physician, respectively; from the Service of Dr. Chas. F. Hamilton, Department of Medicine, Kings County Hospital, Brooklyn, N. Y.

Submitted October 10, 1935.



A—Constant deformity, indicative of carcinoma. B—Large niche, found at necropsy to correspond to the ulcer of the carcinoma, and to be continuous with the fistula.

tery. The stomach shows a large necrotic ulcerated mass in the pyloric region. On section the edges of the ulcer are undermined and the mass is seen to be composed of firm pearly white tissue. Situated on the greater curvature,  $2\frac{1}{2}$  inches proximal to the pylorus, is a fistulous opening into the adherent transverse colon, of about  $\frac{3}{4}$  inch diameter. There is also a small perforation (3 mm.) on the anterior surface of the stomach, accounting for the general peritonitis." Microscopically the tumor was composed of typical adenocarcinomatous tissue.

**Discussion:** The clinical picture of gastro-colic fistula secondary to carcinoma is fairly characteristic in most cases. The clinical course at first is that of the malignancy. Perforation rarely occurs until the growth is well advanced. There is then usually a rapid progression of the picture with a downhill course. Quick weight loss is associated with moderate to severe pain. A fecal odor is noticed to the breath, especially

associated with eructations. Nausea and vomiting follow. The vomiting occasionally is fecal in character. This symptom is practically pathognomonic of gastro-colic fistula, as it occurs only in this condition, with the exceptions of far advanced low intestinal obstruction, jejuno-colic fistula and duodeno-colic fistula. Another important and characteristic symptom is the sudden onset of diarrhea, as a change from the constipation commonly associated with advanced gastric malignancy. Examination of the stool usually reveals the presence of undigested food. Diarrhea is unrelated to the hydrochloric acid content of the gastric juice, as it occurs in cases with achlorhydria as well as those presenting only a decrease in the acid content. The diarrhea is therefore in all probability due to the introduction of food directly in to the colon, and not to the irritating effect of the acid upon the colonic mucosa.

It is commonly found within one-half hour of the ingestion of food. It is present in most reported cases, although absent in our's. Examination of the patient, in addition to general cachexia, usually reveals the presence of a mass in the abdomen, associated with tenderness and rigidity. Depending upon the size and location of the tumor there may be evidence of distension of the stomach. Similarly if there is sufficient invasion of the colon there may also be evidence of distension of the proximal half of this viscus, as well. Fever is a common observation.

**Laboratory findings:** Examination of gastric contents, vomitus, and stool are often of the greatest significance, allowing a clinical diagnosis to be made. The stool in the typical case is foul and diarrheal and contains blood and food particles. If the latter can be identified and the time of their ingestion is known, the discovery of a complete passage through the alimentary canal in two-three hours is of the greatest importance. The gastric contents, in addition to the findings of an advanced malignancy, often show the presence of gross fecal matter. Of all laboratory procedures, however, the X-ray examinations are of the greatest value. These studies reveal the presence of a large gastric neoplasm, at least partially affecting the greater curvature. In most cases, the fistula can be visualized with the fluoroscopy or the stomach plate. In others the colon is seen to contain the barium a few minutes after it has been given by mouth, with no sign of it in the small bowel. In a certain number of cases the fistula either is intermittently closed or, due to a valve-like action, is patent only from below. Such cases will show barium enema is given. The portion of the colon involved is often irregular, with a filling defect. Due to temporary blockage of the fistula, when small, by food, feces or fragments of tumor tissue, the connection may not be visualized by roentgen study.

**Pathology:** The cause for the development of a gastro-colic fistula is the slow perforation of a gastric carcinoma, with walling off rather than acute spreading. The greater curvature is practically always involved and the colon in its splenic flexure or distal half of the transverse portion. Although the fistula is usually short and direct it may be long and tortuous. Its diameter



varies from a few mm. to several cm.

**Diagnosis and Differential Diagnosis:** Fecal vomiting or the sudden appearance of diarrhea, associated with food particles in stool, in a known case of gastric malignancy is practically pathognomonic. Many cases have been misdiagnosed at first, either as non-perforated carcinoma, or as non-malignant disease of the gastro-intestinal tract (typhoid, dysentery, ulcerative colitis, etc.) Apart from careful X-ray study, the use of colored dye substances is of value. Charcoal, methylene blue and carmine red may be given by mouth and searched for in

the stools (if diarrheal) or in the enema washings, one, two and three hours afterward; if this is unsuccessful the same substances may be given by enema and looked for in the gastric washings.

**Treatment:** Gastro-colic fistula, when secondary to tumor, usually is inoperable, but the surgeon must decide this in relation to the individual patient.

**Summary:** Spontaneous gastro-colic fistulae result from perforation of gastric tumors into the colon, or from perforation of colonic tumors into the stomach. A case of the former is presented; it was diagnosed clinically. In arriving at a

diagnosis, diarrhea, fecal vomiting, and sudden downhill course are of extreme value. Roentgenographic studies are usually pathognomonic. Treatment is usually palliative.

#### REFERENCES

1. Haller: Quoted by Friedenwald and Feldman (6b).
2. Zweig: *Ibid.*
3. Brinton: "Lectures on Diseases of the Stomach." Phila., p. 218, 1865.
4. White: 1a Allbutt-Rolleston's System of Medicine, Vol. 3, p. 507, 1910.
5. Smithies: "Carcinoma of the Stomach." Phila., Saunders, p. 101, 1916.
6. Friedenwald and Feldman: (a) *Amer. Jour. Med. Sci.*, Vol. 148, p. 1914. (b) "Internat. Clinics," Vol. 4, p. 28, Dec., 1933.
7. Boerhoeve: Quoted by Friedenwald and Feldman (6b).
8. Verbrugge: Coll. Papers of Mayo Clinic, Vol. 16, p. 104, 1924.
9. Balfour and Down: "Surg. Clla. N. A." Vol. 2, p. 735, Aug., 1931.

## Urogenital Symptoms Referable to Intra-Abdominal Disease\*

By

CHAS. GORDON HEYD, B.A., M.D., F.A.C.S.  
NEW YORK, NEW YORK

THE urogenital system is placed behind a broad curtain of peritoneum. It is not surprising that disabilities and infections of this system should invoke symptoms that are referable to disease of the intra-abdominal organs. In like measure and perhaps more frequently pathological changes in the intra-abdominal organs may initiate symptoms that are referred to the urogenital system.

The most common cause of acute abdominal pain is appendicitis and thereafter in the order of frequency occur cholecystitis, perforated gastroduodenal ulcer, acute pelvic conditions — ruptured extra-uterine pregnancy, twisted ovarian cystoma, salpingitis; acute hematogenous infection of the kidney, acute diverticulitis and mesenteric vascular occlusion.

The microscopic presence of blood in the urine may be part of any pathological process of the genito-urinary apparatus but the presence of any acute abdominal inflammation in proximity to the kidney, ureter or bladder may also occasion microscopic blood.

The last paper written by Maurice Richardson of Boston was entitled

\*Read before the Joint Session of the Surgical and Genito-Urinary Sections of the New York Academy of Medicine, New York. Submitted November 22, 1935.

"The Error of Overlooking Ureteral Stone Under a Diagnosis of Appendicitis," and Connell records two cases with a mass in the pelvis and a distended bladder filled with bloody urine. Laparotomy in both instances disclosed a gangrenous appendix in contact with the fundus of the bladder.

A few years ago one of the most celebrated malpractice suits brought into court in this State hinged upon this dual mechanism of symptomatology. The surgeon had made a tentative diagnosis of suppurative appendicitis or "an infection in and about the kidney." A laparotomy for an appendectomy revealed no adequate pathology to explain the symptoms. The surgeon thereupon exposed the right kidney and drained an infected renal cyst. The claim for malpractice was based upon an alleged error in diagnosis together with assault against the person of the patient.

When there is symptomatic interrelationship between abdominal and urogenital pathology the diagnostic problem is a difficult one. Many years ago Riedel described a jaundice due to right-sided nephroptosis and the designation of Riedel's lobe gave a medical eponym that has persisted in abdominal symptomatology.

Pathological conditions of the right side of the abdomen and more particularly the right upper quadrant would many times simulate renal pathology and more frequently diseases of the urogenital system may suggest clinical entities of the gall bladder, gastro-duodenal segment, appendix and affections of the large intestine. The urgency of the surgical indication in many of the affections of the right side of the abdomen is such that time does not permit of a thorough investigation of the various organs concerned in the symptomatology of this region of the abdomen and while it is granted that extended study would differentiate most affections of the gall bladder, stomach, pancreas, duodenum, appendix and kidney, yet the very acuteness of the manifestations of these affections is such that they present a confusing diagnostic picture.

The symptomatic evolution of acute appendicitis is precise, definite and sequential. There occurs a certain number of cases of acute appendicitis wherein the urogenital symptoms are prominent. A reasonable proportion of the appendices lie retroperitoneally and occasionally are placed with a covering of peritoneum in close proximity to the lower pole of the kidney. A perforation of such



a retroperitoneally placed appendix will invoke all the mechanisms of a perinephritic abscess. In the presence of urinary symptoms rigidity of the right leg due to spasm of the iliopsoas muscle is a physical finding that while infrequent is by no means rare. If a silver dollar were laid one inch to the right and an inch and a half above the navel, it would roughly cover an area of great pathological incidence. The periphery of the silver dollar would embrace the pyloroduodenal area, enclose the fundus of the gall bladder and overlie the superior pole and the upper portion of the pelvis of the right kidney. In addition, it would cover the head of the pancreas and the junction of the common and pancreatic ducts. On its inner periphery it would overlie the vena cava, the superior mesenteric artery and vein, together with the loose retroperitoneal tissue and the retroperitoneal lymph glands. Below the lower border of this imaginary dollar would be the ileocecal angle, rich in its lymphatic glands, and also the lymphatics between the posterior surface of the cecum and the pelvis of the right kidney.

The mechanism of biliary colic due to calculus and that of ureteral colic due to calculus is fundamentally the same. There is the sudden arrest of a passage of fluid from a superior to a lower level. The secretion continues behind the obstruction and there is invoked a remarkable degree of hyperperistalsis and hydrostatic pressure in the attempt to dislodge the obstructing calculus. The onset of symptoms is sudden, dramatic and intense. The history, sex and anatomical distribution of pain usually allow of diagnostic differentiation but occasionally even the X-ray interpretation is dubious.

Another clinical picture that deserves consideration is the similarity of symptoms between the stone in the common duct without jaundice and a calculus of the right kidney. The attacks may be similar, the X-ray examination may expose a shadow and yet the pain may be definitely referable to the area of the upper pole of the right kidney. The transverse localization of upper abdominal pain in disease of the pancreas is not without its possible implication of kidney disease. Moreover, an obstructive condition at the outlet of the pelvis of the kidney may produce such an intense visceral reaction as to simulate in detail an

acute intestinal obstruction. A clinical picture of intestinal obstruction occurring in a virginal or nonoperative abdomen should always require careful diagnostic scrutiny as to the possibility of kidney disease. An infection arising from infected uterine contents may spread through the parametrial lymphatics and produce a retroperitoneal lymphangitis which will simulate to a remarkable degree a hematogenous infection of the kidney.

#### CASE REPORTS

Case No. 1. A young woman, twenty-eight years of age, entered the hospital, with a temperature of 103°, pulse 120, anxious, worried facies, vomiting, with moderate generalized abdominal distention and pain in the left hypogastrium. The blood culture was negative, the white differential count revealed 21,000 leucocytes, 19% polymorphonuclear. The routine urinary examination was negative. The patient had never been operated upon. A clinical diagnosis was made of a pneumococcal peritonitis, largely upon the absence of any—at that time known—etiological factor. Gynecological examination by two different consultants recorded the pelvis negative. Under expectant treatment the patient slowly improved and after five days complained of intense pain in the region of the left kidney and was exquisitely sensitive on mass percussion over the left renal region. Cystoscopic examinations were made and after careful diagnostic scrutiny, the possibility of either kidney as the site of disability was ruled out. After protracted convalescence the patient made a satisfactory recovery and it was then revealed that some five days before admission to the hospital there had been a forceful emptying of the uterus for a supposed six weeks' pregnancy. It seemed evident in retrospect that the atrium of infection was by the lymphatic system of the parametrium and that a retroperitoneal lymphangitis was responsible for the urogenital symptoms.

Acute mesenteric vascular occlusion may well simulate the characteristic symptoms of Dietl's crisis and the surgical record of acute hematogenous infection of the kidney—Brewer's septic infarct of the kidney—indicates the atmosphere of doubt that may surround this condition in view of the fact that in Brewer's original thirteen cases laparotomy was performed three times and in

Cobb's eight cases laparotomy was done in three instances.

One of the most confusing clinical pictures is the development of a subphrenic abscess secondary to a laparotomy for some infected condition within the abdomen. The continuation of temperature, the varying degree of dehydration and the almost uniform absence of pain tend to make localization of a subphrenic abscess one of extreme clinical difficulty. The degree with which an intraperitoneal but subdiaphragmatic abscess may simulate a perinephritic abscess is a factor of recorded experience.

The perforation of a neoplasm at the hepatic or splenic flexure will simulate a primary neoplasm of the kidney. There will be fixation of the colonic mass to the perirenal tissues, as well as frequency of urination and the presence of red blood cells. The precision of X-ray diagnosis and the almost absolute precision of urogenital diagnostic measures make it possible to allocate the anatomical identity of the neoplasm. Of much greater diagnostic difficulty is the patient with a known pyuria and an intra-abdominal affection. It is well to recall that statistically the right-sided bacilluria is more frequent than the left and according to Bishop is in proportion of ten right to one left. The lymphatic route from the cecum to the pelvis of the right kidney is short and direct. Pathological conditions involving the terminal ileum, the cecum or the appendix, are factors that contribute to the development of right-sided urogenital symptoms.

Case No. 2. A child five years of age, male, entered the hospital with a temperature of 105°, with marked frequency of urination, moderately severe diarrhea and a mass in the right loin. There was a history of the child crying out suddenly, being unable to pass urine, but after twelve hours beginning to dribble urine. The child was treated at home and was brought to the hospital, when the temperature rose rapidly and the child complained of abdominal pain. Aside from the mass the most obvious symptom was the urinary dribble. This was due to seepage from over-tension of the bladder, which was obvious on catheterization. In addition to palpation, a flat X-ray revealed a mass overlying the right ureter and bladder. At laparotomy

# Avoiding Gall Stone Precipitation

IT has been authoritatively stated that if a patient is being treated for Gall Stones, in which case temperature is of long duration and the patient is refusing food, he should be given, three times a day, BILE SALTS.

For nearly a quarter of a century the one bile salts that has been generally accepted because of its efficacy is

## TAUROCOL BILE SALTS TABLETS



TAUROCOL is a combination of bile salts, extracts of cascara sagrada, phenolphthalein and aromatics and is an agent recognized by the medical profession and widely prescribed for about a quarter of a century.

### TAUROCOL COMPOUND TABLETS

In combination with digestive ferments (pepsin, pancreatin, extract nux vomica) are especially indicated for intestinal indigestion and auto-intoxication.

Insufficient gastric and intestinal digestion is frequently associated with biliary sluggishness. In such conditions addition of digestive ferments is of advantage.

The Paul Plessner Co.

Detroit - - - Michigan

One of the most masterful articles ever written on Gall Stones appeared in the American Journal of Digestive Diseases and Nutrition, November, 1935 Issue, from the pen of A. J. Delario, M.D., of Paterson, New Jersey. A complete reprint of this article, prettily and graphically illustrated, may be secured by you by filling in the coupon below.

#### THE PAUL PLESSNER COMPANY

3538 Brooklyn Avenue,  
Detroit, Michigan.

J. D. 2-36

[ ] Send me reprint of Dr. Delario's Article on Gall Stones.

[ ] Send me samples and literature on TAUROCOL BILE SALTS TABLETS.

[ ] Send me samples of NEO-TAUROCOL TABLETS.

[ ] Send me samples of TAUROCOL COMPOUND TABLETS.

Name \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_

an appendiceal abscess was revealed.

The presence of a palpable mass to one side or the other of the median line and arising from either the pancreas as a pancreatic cyst, or from the retroperitoneal lymph glands as a retroperitoneal sarcoma or Hodgkins disease, invites consideration of kidney disease.

Endometrioma is apparently not as infrequent as is generally supposed. The name is applied to various tumors containing endometrium and which have the property of growth outside of the uterus and on almost any of the intra-abdominal viscera. They have a predilection for multiple endometrial transplants on the sigmoid, in the cul-de-sac and on the wall of the bladder. Masson recently has drawn attention to vesical irritability, increased frequency of urination and hematuria, and with occasional dysuria and macroscopic hematuria.

It is a matter of clinical observation that neoplasms of the right side of the colon generally develop few obstructive symptoms, whereas neoplasms of the left colon in the course of their growth do develop obstructive symptoms. The addition of spasm to a neoplasm of the sigmoid may produce such a similitude of symptoms as to suggest a left-sided renal calculus. Acute perforating diverticulitis or, as it is sometimes called "left-sided appendicitis," not infrequently is associated with manifest urogenital symptoms. Since this condition usually occurs in the more mature or elderly male patients, they very frequently have prostatic and bladder symptoms by reason of intrinsic changes in the bladder and prostate. However, approximately ten per cent of those patients consult a physician for their urinary symptoms. Anatomically, the perforation will occur extraperitoneally as frequently as it will within the peritoneal cavity and the presence of an infective material in the retroperitoneal space below the sigmoid and impinging upon the ureter and bladder produces an associated ureteritis and cystitis with vesical symptoms.

The presence of jaundice may produce a nephrosis and the nitrogenous retention primarily due to the pathological factors producing the jaundice is very apt to be construed as due to renal damage.

Elsewhere we have described an infrequent complication in gall bladder surgery characterized by a



*Dear Doctor:*

Routine, pre-operative cleansing of the bowels is a recognized procedure. Enemas have had the preference in most cases because cathartics may not evacuate completely, and may cause distressing symptoms and pre-operative fatigue.

May we suggest that you try TAXOL a few days before the operation; one, two, or more b.i.d., or t.i.d., according to need, because the dosage varies. You will find that TAXOL achieves the desired results without untoward symptoms.

X-ray studies testify to the completeness of the evacuation with TAXOL. Why not try it? Even enemas have their inconveniences.

*Very respectfully yours,*

**LOBICA LABORATORIES**

1841 BROADWAY

NEW YORK



LOBICA LABORATORIES, 1841 Broadway, N. Y. C.  
I would like a supply of TAXOL, also literature.

M. D.

D. D. 2-36

gradual cessation of urinary secretion, a rise in the urea-nitrogen in the blood and a fatal termination. These patients may have associated with their terminal complication acute abdominal pain, distention, severe vomiting and fever. Clinical examination of the blood shows a normal icteric index and an ascending scale of urea-nitrogen. The death certificate is usually signed "uremia." It is our opinion that uremia does not occur in the manner herewith described as nitrogen retention, per se, does not necessarily

indicate an insufficient kidney function. A dehydration equal to a fluid loss in relation to total body weight of five per cent will occasion a pathological rise in the non-protein nitrogen of the blood similar to that found in many cases of chronic nephritis. It can be explained on the basis of the concentration of the blood due to the loss of water by dehydration, as well as an increased protein catabolism. Increasing study has shown that the hepatic complications may mimicry uremia with striking fidelity.

## ABSTRACTS

WANGENSTEEN, O. H.

*Repair of Recurrent and Difficult Hernias and Other Large Defects of the Abdominal Wall Employing the Iliotibial Tract of Fascia Lata as a Pedicle Flap.* S. G. and O., Vol. LIX, No. 5, pp. 766-780, Nov., 1934.

The operative procedure which the Author presents is a new application of the principle of transplantation of tissue with nerve and blood supply intact—the pedicle transplant. The transplanted tissue is the iliotibial tract and fascia rotated on the Tensor Fascia Lata Muscle as the pedicle from which the nerve and blood supply are transmitted.

Pre-operatively the skin is prepared by washing with soap and water, followed by the application of alcohol, benzine, ether, and finally, tincture of iodine applied in two coats. The iodine is later removed by Richardson's solution. In patients having large hernias, the Author inserts a Levine tube with multiple perforations into the stomach the night before operation, and applies suction to it post-operatively.

A vertical incision tapering laterally is made on the antero-lateral surface of the thigh, and the desired area of fascia lata exposed by undercutting the skin. This area of fascia is incised anteriorly, posteriorly and inferiorly, after which it is dissected away from the muscles and the intermuscular septum from below upwards leaving it suspended from the muscle *tensor fascia lata*. The deep surface of this fascia is smooth, while the superficial surface is covered by a variable amount of fat. In the repair of defects of the abdominal wall this flap is pulled up beneath Poupart's ligament with the fatty side down, and fixed in place with sutures of chromicised catgut. In the repair of hernias the flap is best slung over Poupart's ligament. In incisional hernias the flap is used as a patch over the site of suture, while in inguinal and femoral hernias the flap is intimately incorporated with the adjacent tissues in the closure. In certain instances of femoral hernia the Author has split the flap using part of it beneath Poupart's ligament, and part above.

Meticulous care is observed to obtain absolute haemostasis in both wounds; dead spaces are effectually obliterated. A subcutaneous drain is left in place for 24 to 48 hours in larger hernias. No attempt is made to close the fascial defect in the thigh. No functional disability in the thigh or leg is complained

## IN FECAL PUTREFACTION

# • KARICIN •



In the treatment of intestinal toxemia, putrefaction, mucous colitis, Karicin helps to

Detoxify the toxins of intestinal flora

Check fermentation

Reduce flatus

Soothe irritated mucosa

**DOSAGE:** The average dose of Karicin is a tablespoonful three times daily, taken in water or milk, at least one hour before or one hour after meals.

**SIZE:** Karicin is available in 10 oz. wide-mouthed bottles.

SEND FOR CLINICAL TRIAL SAMPLE.

**THE WM. S. MERRELL COMPANY**  
CINCINNATI, U. S. A.

# STIMULATING NORMAL PERISTALSIS BY DISTENTION

ASCENDING COLON—NORMAL CONTRACTIONS

Contractions  
without  
Mucilose



11.45. Min

Dog # 206

Right of Transverse Colon

11.50. Min

Hyper-reflexic - Colon Tonic 24 hrs. After Feeding  
Maximal by Mouth



Contractions  
24 hours after  
feeding with  
Mucilose

11.55. Min

Dog # 206  
Dec. 16, 1927

## MUCILOSE

(STEARNS)

**Laboratory Evidence**—Conclusive tests on dogs show this inert, non-irritating, bulk-supplying, bland lubricant will result in large-formed, soft stools.

**Clinical Confirmation**—Mucilose has amply confirmed its value as a non-irritating stimulant to the spastic colon, by physiologic distention.

### EFFECTIVE—EASY TO TAKE—ECONOMICAL

Mucilose is obtained from the *Plantago loeflingii*. Supplies bland, non-irritating bulk without leakage, without impairing digestion.

**FREDERICK STEARNS  
& COMPANY**

DETROIT NEW YORK KANSAS CITY  
SAN FRANCISCO WINDSOR, ONTARIO  
SYDNEY, AUSTRALIA

FREDERICK STEARNS & COMPANY  
Detroit, Michigan Dept. D.D.2  
Please send me a supply of Mucilose for clinical test.

Dr. ....

Address .....

City ..... State .....

of because of transfer of the iliotibial tract.

The Author reports 14 cases in detail. There was one death apparently from fat emboli, and one recurrence. Eight figures and a bibliography accompany the article.

N. M. Percy, Chicago.

MATHEWS, ROBERT W., AND SCHNABEL, TRUMAN, G.

*Primary Esophageal Carcinoma, With Especial Reference to a Non-stenosing Variety.* J. A. M. A., 105:1591, Nov. 16, 1935.

In a group of 108 patients with carcinoma of the esophagus that came to autopsy, twenty-two exhibited a non-stenosing variety of lesion. The usual symptoms of dysphagia, pain, regurgitation of food and vomiting were not prominent in this nonstenosing group. The outstanding complaints were weight loss, pains in the chest, vomiting, cough, hoarseness and weakness. Dysphagia was relatively infrequent. The clinical course of the nonstenosing group was one-third as long as that of the stenosing group.

Röntgen examination should be followed by esophagoscopy and tissue obtained for biopsy in suspected cases. The fact that esophageal carcinoma may not produce stenosis must not be overlooked.

Francis D. Murphy, Milwaukee.

ZOLLINGER, R.

*Uretero-Intestinal Anastomoses. The Use of Mechanical Anastomosing Apparatus.* S. G. and O., Vol. LIX, No. 5, pp. 796-805, Nov., 1934.

The Author presents a technique of uretero-intestinal anastomosis in which a modification of the ordinary snap dress button is used. A free flow of urine postoperatively is allowed, and the ureter is protected from infection ascending by its lumen, or its lymphatics.

The male portion of the button is placed in the previously cleansed rectum, and held in place by means of a dressing forcep. After the abdomen has been opened and the mucosa prepared, the button is grasped by the thumb and the fore-finger, and the clamp in the rectum is released by the unsterile assistant. The sterile portion of the button, with a small catheter attached and sutures passed through the top of the button for anchorage of the ureter, is then pressed into position. One should attempt to allow just enough room for the mucosa to be pinched tightly, but not cut off at the time of anastomosis. The buttons are not entirely satisfactory in that respect: a screw button for that purpose should be constructed. About six inches of a No. 7 whistle tip catheter is used on the sterile portion of the button. After the button is pressed to-

gether, sterile saline should be injected into the catheter to make sure that a free communication to the outside exists. The short catheter is then threaded into the ureter, and the end of the ureter is fastened to the sterile portion of the button by the sutures previously put in place. The ends of the ureter projecting beyond the button are sutured to the mucosa of the bowel thereby insuring the presence of viable ureter beyond the small opening made when the button is removed. Immediately, and for a week after the operation, the animals were given 500 to 1000 cubic centimeters of saline intravenously to insure a continuous flow of urine.

By this technique the Author has obtained excellent results in dogs. The factors which contributed to the failures encountered could be readily controlled in the human, and even better results expected there.

A discussion of the methods previously used to accomplish uretero-intestinal anastomoses is given.

Twenty-one figures accompany the article.

N. M. Percy, Chicago.

MEYER, JACOB, SCHEMAN, LOUIS AND NECHELAS, N.

*Action of Oil of Peppermint on the Secretion and Motility of the Stomach in Man.* Arc. Int. Med., Vol. 56, No. 1, p. 88, July, 1935.

Oil of peppermint, when given by itself or with a secretory stimulant, depresses the secretion of acid by the stomach. The mechanism of this action, the Authors state, is unexplainable.

In dogs the action seems to be local, on the mucosa.

In patients suffering from peptic ulcer, the secretion of acid of the stomach at rest is depressed or inhibited by Oil of peppermint. When this secretion was abundant, as after the administration of alcohol or histamine it was diminished or completely abolished by the Oil of peppermint.

The dose administered was from one to two c.c.

A. N. Aaron, Buffalo.

FITTS, JOHN B.

*Motor and Secretory Dysfunction of the Gastro-Intestinal Tract and the Vitamin B. Factor: A Clinical Study.* South. Med. Jour., 28:920-923, Oct., 1935.

The triad, "gas, belching, and fullness after meals," heard by the surgeon as well as the internist is ascribed, in the absence of an organic pyloric cause, to delayed emptying time resulting from atonic gastric musculature. Other symptoms accompanying these include constipation, nausea, regurgitation and headache. A physical sign of importance is a successive gastric splash with which there is frequently found a pal-

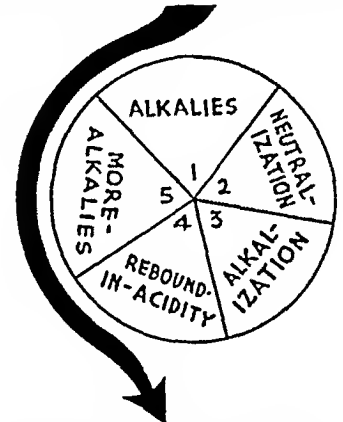
## NO NEED NOW FOR USING TOXIC ALKALI

**I**N the treatment of peptic ulcer and other conditions where the neutralization of gastric HCL is desirable the alkalies can be satisfactorily replaced.

**Y**OU can guard against the toxic effects of sodium bicarbonate, magnesium oxide, calcium carbonate and the like by depending upon TRI-CALSATE, the buffered neutral antacid.

**N**ON-TOXIC and non-irritating, TRI-CALSATE may be safely prescribed even in cases which are complicated with a bowel or kidney irritation.

**T**RY TRI-CALSATE. You will find that it gives you all of the advantages of the alkaline antacids without any of their disadvantages.



You can avoid the vicious circle of alkali neutralization when you prescribe

## TRI-CALSATE

Available on prescription or direct in 4 oz. and 16 oz. bottles.

Use the coupon or write us for a trial supply and literature.

F. H. Paxton & Sons, Inc.  
451 E. Ohio St.  
Chicago, Ill.

Please send me literature and a trial supply of Tri-Calsate.

Name.....

Address.....

City & State.....



# For the Food Finicky Patient



THE sickly and undernourished are often finicky about their food, particularly children, during the winter "shut-in" period. They need something to tempt the appetite, something that will be easily digested and will be highly nutritious.

Ovaltine helps you to answer this problem very effectively. Children and adults delight in its enticing flavor, and Ovaltine actually adds important food elements to plain milk or, as a physician once aptly said, "It makes milk a square meal."

Ovaltine provides maximum nutritional value with minimum functional strain. It provides a good additional source of the essential mineral elements, notably calcium, iron and phosphorus, and of the Vitamins A, B, G and D, all of vital importance in the promotion and maintenance of robust health.

Ovaltine is invaluable for its building-up properties during convalescence, in wasting diseases, for the undernourished and therefore frequently nervous child, and wherever hyperalimentation is desired.

## Fill in the Coupon for Professional Sample

Why not let us send you a trial supply of Ovaltine? If you are a physician, dentist, nurse or dietitian, you are entitled to a regular package. Send coupon together with your card, letterhead or other indication of your professional standing.

# OVALTINE

*The Swiss Food-Drink*

Manufactured under license in U.S.A.  
according to original Swiss formula.

**This offer is limited only to practicing physicians,  
dentists, nurses and dietitians**

THE WANDER COMPANY  
180 No. Michigan Ave.  
Chicago, Ill.

Dept. D.N.2

Please send me, without charge, a regular size package of Ovaltine.  
Evidence of my professional standing is enclosed.

Dr. ....

Address .....

City..... State.....

Canadian subscribers should address coupons to  
A. Wander, Ltd., Elmwood Park, Peterborough, Ont.

pable cecum and iliac colon. X-ray and laboratory examination reveal evidence of ptosis, hypo and achlorhydria, splastic colon with stasis, subnutritional states and mild hypothyroidism. Chronicity and resistance to treatment is typical. Accompanying gall bladder disease is quite rare.

It is believed that these cases are the result of a deficiency of the B antineuritic factor of vitamin B. This deficiency is attributed to the downward trend in the use of meat and cereal with the corresponding increase in the use of sugar. Most cereals now used are de-

germinated and white bread is of questionable vitamin B content. A series of 75 cases constituted the clinical study of this report. In commenting on the fact that 50 per cent of the patients had had appendectomy performed, attention was directed to the effect of vitamin B deficiency on the integrity of lymphoid tissue.

Excellent results followed the administration of vitamin B. However, since sufficient bulky foods could not be consumed because of limited digestive capacity, it was necessary to administer vitamin B in a concentrated form of

wheat germ either the English product "bemax" or the American preparation "embo" being found satisfactory.

J. Duffy Hancock, Louisville.

STROMBERGER, L.

*La Colibacillose. Etude clinique et therapeutique. Masson et Cie, Paris.*

This monograph of 248 pages presents a clinical and therapeutic study of the problem. It sets forth the pathologic manifestations of the common colon bacillus. The Author states that this organism produces three groups of symptoms (1) those concerning the urinary tract with definite pathology, (2) those concerning visceral localization, (3) and those in which other pathology exists, aggravated by the presence of the colon bacillus.

He discusses portal of entry and etiology from the standpoint of lesions of the upper and lower urinary tract and predisposing causes of the receptivity of the organism to this bacterium.

He deals with general, digestive, nervous, endocrine, blood, joint, and skin symptoms.

Colon bacilluria may result in septicemia, pulmonary lesions, hematuria, and other visceral manifestations.

The treatment has many ramifications. It concerns prophylactic measures. Diet is of great importance. Pyelitis and pyelonephritis must be considered. Intestinal manifestations are significant. Urinary antiseptics and mineral waters are used. Finally, vaccine and serum therapy may be indicated.

This treatise should be interesting and instructive reading for both the gastro-enterologist as well as the urologist.

J. Arnold Barger, Rochester, Minn.

MACGUIRE, D. P.

*Carcinoma of the Colon. S. G. and O., Vol. LIX, No. 5, pp. 762-765, Nov., 1934.*

The Author presents a surgical procedure for carcinoma of the colon in which the growth is excised without cutting or clamping the bowel intraperitoneally. The patient is prepared by a preliminary cecostomy, blood transfusions and the administration of fluids. An indwelling catheter is put in place. A median or left rectus incision is made, and the mesentery is resected from a point above the growth down through the peritoneal reflection. The abdomen is temporarily closed, and the patient placed in the lithotomy position. The perineal incision is made with a cautery, and is continued until sufficient rectum extrudes so that a rubber glove can completely cover the lower bowel. Having dissected up to the peritoneal reflection the abdomen is re-entered, the peritoneal reflection dissected, and the entire segment of bowel

## THE IDEAL LAXATIVE



Easy To Take

Gentle Action

No Leakage

Softens the  
Fecal Mass

No Dehydration

## HALEY'S M-O

An Emulsion of Milk of Magnesia and Pure Mineral Oil presents the smooth, laxative-antacid properties of magma magnesiae and the lubricating, fecal-softening effect of petrolatum, in a palatable, stable emulsion.

Supplied in 8-oz., 16-oz. and 32-oz. bottles.

DOSE: 1-2 tablespoonfuls, before breakfast and at bedtime.

SAMPLE TO PHYSICIANS, ON REQUEST

The Chas. H. Phillips Chemical Co.  
170 Varick St. New York, N. Y.

# ✓ Check THE HYPERMOTILE BOWEL with **KAOMAGMA**

Diarrheas of whatever origin, the so-called "unstable colon," dysentery of amebic or bacterial origin, "ptomaine poisoning," are relieved promptly, as are simple colitis, infectious colitis and similar conditions.

Kaomagma adsorbs bacterial toxins and products of putrefaction, soothes the inflamed mucosa, promptly consolidates liquid feces and reduces too frequent stools to normal.

Kaomagma is an emulsoid of finest medicinal kaolin dispersed in Alumina Gel.

Kaomagma Plain and Kaomagma with Mineral Oil are available in 12-ounce bottles at your prescription pharmacy.

LITERATURE AND SAMPLES TO PHYSICIANS ON REQUEST



**JOHN WYETH & BROTHER, INCORPORATED**  
PHILADELPHIA, PA. • WALKERVILLE, ONT.

carried out of the abdomen through a left sided colostomy incision. The peritoneal reflection is closed, and the incision in the abdomen is also closed in the usual manner. The perineal wound is packed and sutured. The end of the bowel containing the tumor is cut between clamps. By these manipulations there is very little chance of infection and peritonitis.

In those cases of tumor of the left colon the Author prefers a modified Mikulicz and Paul operation after preliminary cecostomy. More colon may be

drawn out of the abdomen if the phrenico-colic ligament is cut fairly high up.

When dealing with malignant tumors in the right half of the colon the Author uses the Paul-Mikulicz type of operation, the terminal ileum being used as one barrel and the hepatic flexure of the colon as the other. In no case is the bowel sutured to the parietal peritoneum.

The Author believes that no operation in which the large bowel is clamped can properly be called aseptic since

many microbes are spilled into the peritoneal cavity every time clamps are applied across the lumen of the bowel.

Twelve figures accompany the article.

N. M. Percy, Chicago.

SANDERS, L. C.

*"The Colon—A Consideration of Its Important Diseases and Disordered Functions."* *South. Med. Jour.*, 28:848-851, Sept., 1935.

Differentiation of the disorders of the colon is simplified by considering them under the following classification: first, organic disease of the colon, including new growths, parasitic diseases, infections, and anomalies, and secondly, functional disorders of the colon including neurogenic, allergic, dietetic, and reflex factors. The large number of apparently border line conditions can usually be placed in one of these groups after sufficient study and observation. An excellent concise symptomatology is given for each group. The Author recognizes the difficulty involved in treating the functional disorders as calling upon the art as well as the science of medicine.

J. Duffy Hancock, Louisville.

BROWN, B. W.

*Results and Dangers in the Treatment of Amebiasis: A Summary of Fifteen Years' Clinical Experience at the Mayo Clinic.* *J. A. M. A.*, 105:1219, Oct. 26, 1935.

The Author reviews the treatment of amebiasis in 834 cases. In 523 of these cases information as to the results of treatment was secured later. Emetine hydrochloride seems to be a standby throughout the entire period. With the introduction of treparsol and acetarsone, the use of emetine hydrochloride decreased somewhat. At the clinic emetine hydrochloride has been administered subcutaneously. The distressing complications of emetine therapy are peripheral neuritis or palsy and cardiovascular disturbances. At the clinic emetine is used to control acute manifestations of the disease. Reactions are very few. If the use of the dose of ten grains of emetine hydrochloride subcutaneously in a month's time is not exceeded, the danger of reaction is less than one per cent. Of the organic arsenicals arsphenamine, acetarsone and treparsol have been used at the clinic. Acetarsone has been thoroughly tried and there have been no deaths in 232 cases. There were two cases of neuritis and thirteen cases of toxic erythema. Treparsol was given to 301 patients. There were eight cases of toxic erythema, and there were no cases of neuritis. One patient had nausea and vomiting after taking one gram.

Chiniofon, also known as yatren or anayodin, has been regarded favorably at the clinic. Increase in diarrhea is rather frequent with the usual dosage of three grams daily. The drug was

## TILDEN Has Kept Faith With Physicians

# FIROLYPTOL (TILDEN)

A FREQUENT prescription in *Strumous Diatheses* for many generations has been the Firolyptol made by The Tilden Company. The composition of the product has been imparted only to physicians and consists essentially of the Bromides, Phosphates, Iodides, Eucalyptol, Ol. Gossypii Sem. Purificat. combined in a manner exclusive with Tilden. The quantities are sufficient and have full therapeutic effect when taken in dosages and in a manner indicated in the condition. There is ready subsidence of the symptoms of Pain, Discomfort, Nervousness and Metabolic Disturbance often observed in this branch of treatment.

The continued use of Firolyptol (Tilden) for generations and its increasing value as an ethical prescription specialty have been appreciated by the medical profession as its increased use indicates.

The public sees no Tilden advertising since an appeal for consideration of these ethical products is made only direct to the medical profession and through no other source than the best medical journals. All Tilden products are labeled only with the name and composition as required by the federal law and do not bear any therapeutic claims except in the rare cases where these are necessary for the information of the physician and in this case they are written in language not intelligible to the laity.

The Tilden Company has always been honored to receive requests from physicians who are sincerely interested in making clinical trial of these medical specialties with the view to prescribing or dispensing them.

## RUBIPHEN

*Rubiphen is a childrens' prescription recommended by physicians in Common Colds as an effective sedative and expectorant. It contains Phenobarbital, Sodium Citrate, Ammonium Chloride, and Tincture of Ipecac essentially.*

## THE TILDEN COMPANY

The Oldest Pharmaceutical House in America

NEW LEBANON, N. Y.

A. J. D. D. 2-36

ST. LOUIS, Mo.



## When Acidosis Complicates Disease

Supporting the alkali reserve has become a routine measure in diseases characterized by acidosis. For this purpose, Alka-Zane is extensively used because it supplies the four bases of which the reserve is essentially composed: sodium, potassium, calcium, magnesium. These are made available to the organism in the form of carbonates, citrates and phosphates. Alka-Zane contains no tartrates, lactates, or sulphates, and no sodium chloride. It is a convenient and efficient way to prescribe alkalizing medication that is palatable and easy to take.

*Alka-Zane is supplied in 1½, 4 and 8 ounce bottles. Trial supply sent on request.*

# ALKA-ZANE

---

WILLIAM R. WARNER & CO., 113 West 18th Street, New York City

---

only employed in thirty-seven cases. Conclusions cannot therefore be drawn.

Vioform has been tried in only eighteen cases. There were no difficulties with its use.

The result of the treatment with the drugs is as follows: Emetine failed as a curviture agent in 45 per cent of the cases. Too few results are available in the use of the other drugs for any opinion.

The present method of handling amebiasis at the clinic is as follows:

The patient is given a grain of emetine hydrochloride subcutaneously twice daily for three days; after an interval of a week  $2/3$  grain of emetine is given twice daily for three more days. With the institution of the emetine, four grains of treparsol is administered orally with each meal for four days. If there is no intolerance to arsenic, two more such courses are prescribed with intervals of ten days between. The very ill patient is kept in bed for the first few days. The diet should be bland

and simple, but full and generous diet is begun very rapidly.

If stool tests are positive following this regime, chiniofon is prescribed. Three grams orally per day for a week, and repeated for two or more such courses with a week between courses. Failure after this is followed by one injection of arsphenamine weekly for six weeks and a dram of bismuth subnitrate from three to six times daily during the period.

Francis D. Murphy, Milwaukee.

BEER, EDWIN.

"Diagnostic Study of Obscure Abdominal Complaints." S. G. and O., 61:549-550, Oct., 1935.

In a brief editorial, the Author reminds us of our obligation to give more study to obscure abdominal complaints in order that earlier diagnosis may be made instead of waiting for late obvious clinical signs or resorting to frequently useless exploratory operations. Especial emphasis is attached to the use of X-ray examinations. The three "tubular systems" within the abdomen are studied by a flat picture of the abdomen, an excretory urogram, a gall-bladder series, and a gastro-intestinal series including a barium enema. In those cases where the pathology is not located by these measures and there is an adequate suspicion that the abdominal pains may be referred a lipiodol subarachnoid injection is made for diagnosis and localization of possible spinal cord neoplasm.

J. Duffy Hancock, Louisville.

BLANCK, E. E.

*Peptic Ulcer. An Experimental Study.* S. G. and O., Vol. 61, No. 4, pp. 480-493, Oct., 1935.

The Author performed experiments designed to determine the importance of the presence of bile in inducing experimental peptic ulceration. The experiments were performed on healthy dogs. The first group, consisting of two normal dogs, was sacrificed to serve as control studies. The second group consisted of five dogs with complete external biliary fistulas. The bile as secreted by the liver was collected externally but not fed back to the animals. In the third group of three dogs the bile was fed back to the animals after being mixed with the laboratory stock diet. When the condition of any animal became poor it was sacrificed to insure fresh material for microscopic study.

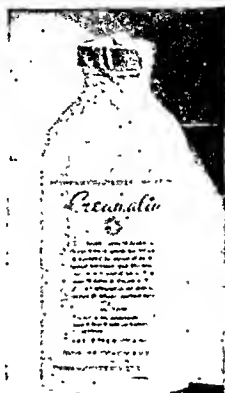
From a careful study of those experiments, the Author concludes that the presence of bile in the diet of the animals prevents the development of gastritis, duodenitis, jejunitis and ulceration which developed in those dogs which received no bile.

Nine figures, a review of the literature and a large bibliography accompany the article.

Nelson M. Percy, Chicago.

# The Logical Treatment for Peptic Ulcer Creamalin

The Specially Prepared  
Colloidal Cream of  
Aluminum Hydroxide



## Because Creamalin

- Neutralizes larger volumes of hydrochloric acid
- Provides prompt relief of pain, nausea and pylorospasm (Usually within 24 to 36 hours)
- Produces no increase of hydrochloric acid secretion
- Avoids all danger of alkalosis
- Is an ideal demulcent and protective
- Is economical and simple to administer

CREAMALIN, therefore, constitutes logical therapy in gastric and duodenal ulcers, especially those that have been resistant to ordinary methods of treatment.

CREAMALIN represents the latest significant advance in the treatment of peptic ulcer and allied conditions. Its efficacy has been demonstrated by competent investigators in thousands of cases of peptic ulcer.

CREAMALIN is a pearly white, amphoteric, colloidal cream of aluminum hydroxide slightly astringent but not unpleasant to the taste. CREAMALIN combines with 14 times its own volume of hydrochloric acid in one hour. The colloid particles in CREAMALIN are dispersed by a special technique which accounts for its unique neutralizing properties.

The merits of CREAMALIN can best be evaluated by critical clinical study. We invite gastro-enterologists to test CREAMALIN in this way. Sufficient material for clinical trial will be sent upon application to

Cleveland Chemical Associates - - Cleveland, Ohio

Kindly send me a supply of Creamalin for clinical investigation.

Dept. D2

Dr.

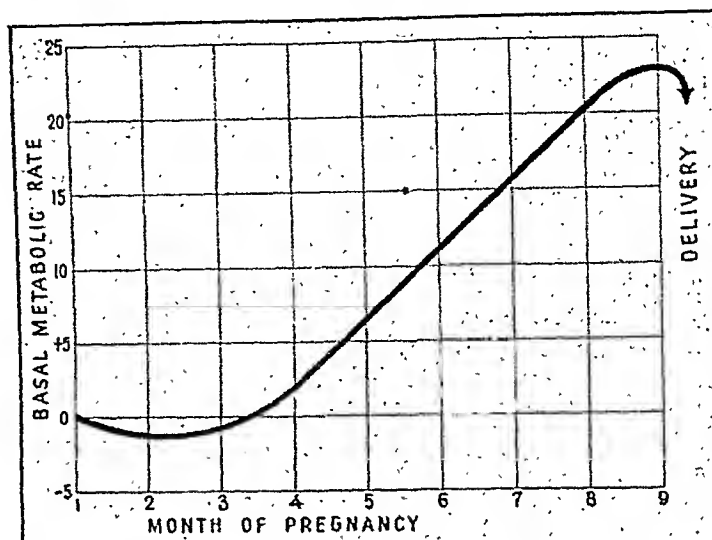
Street and Number

City

State



# PROTECTING THE EXPECTANT MOTHER



**N**ORMAL PREGNANCY has its disturbances. During the first half of pregnancy the woman's metabolic rate is not changed. After the fourth month it gradually increases to 23% above her norm. Caloric increase in the diet is thus necessary after the fourth month.

But vomiting of pregnancy interferes! The condition is looked upon today as a disturbance in carbohydrate metabolism. Upon this assumption is based the present-day treatment by carbohydrate diet. The early introduction of small carbohydrate meals at 3 hour intervals helps prevent this disturbance. Karo added to foods and fluids prevents glycogen depletion and ketosis.

The enlarging of the uterus further produces reflex vomiting and unless carbohydrate is taken throughout the day to maintain the blood sugar at a high level, ketosis results. This aggravates the vomiting, frequently beyond control, because of the inability of the damaged liver in pregnancy to resist ketosis. Karo helps provide the expectant mother with readily assimilated sugars preventive of ketosis. Karo consists of dextrins, maltose and dextrose (with a small percentage of sucrose added for flavor), not readily fermentable, rapidly absorbed and effectively utilized.



Corn Products Consulting Service for Physicians is available for further clinical information regarding Karo. Please Address: Corn Products Sales Company, Dept. D-242 17 Battery Place, New York City.

# A BRIEF REVIEW OF THE RESEARCH ON BRAN

THE Kellogg Company has aided, for some years, research in leading university laboratories. These studies indicate that bran is a wholesome food for normal people, and that the laxative effect of bran is not reduced by continued use. (1)

Laboratory measurements (2) have proved that bran is a good source of vitamin B, and (3) that it is rich in iron.

Independent research has proved that bran corrects constipation due to insufficient "bulk." (4) Further tests have shown that, with some individuals, the "bulk" in fruits and vegetables is largely broken down in the alimentary tract. So bran is often the more effective source of "bulk." (5)

Kellogg's ALL-BRAN is accepted by the American Medical Association Committee on Foods. It is usually more satisfactory for correcting atonic constipation than the continued use of medicines. A few individuals have diseased or highly sensitive intestines. In these cases, any form of "bulk" is inadvisable.

ALL-BRAN is sold by all grocers. Made by Kellogg in Battle Creek.

(1) *The Influence of Bran on the Alimentary Tract*, pages 133-156, *J. Am. Dietetic Assn.*, July, 1932.

(2) *Wheat Bran as a Source of Vitamin B*, pages 368-371, *J. Am. Dietetic Assn.*, March, 1932.

(3) *Factors in Food Influencing Hemoglobin Regeneration*, pages 593-608, *J. Biological Chem.*, June, 1932.

(4) *Laxative Effects of Wheat Bran and "Flushed Bran" in Healthy Men*, pages 1866-1875, *J. Am. Med. Assn.*, May 28, 1932.

(5) *Further Studies on the Use of Wheat Bran as a Laxative*, pages 795-802, *J. Am. Med. Assn.*, March 18, 1933.



## An Intestinal Antiseptic of Proved Performance

Whatever the causal agent of Ulcerative Colitis may be, we know that the intelligent use of Alpha

**ALPHA NAPHCO**  
in water or  
orange juice

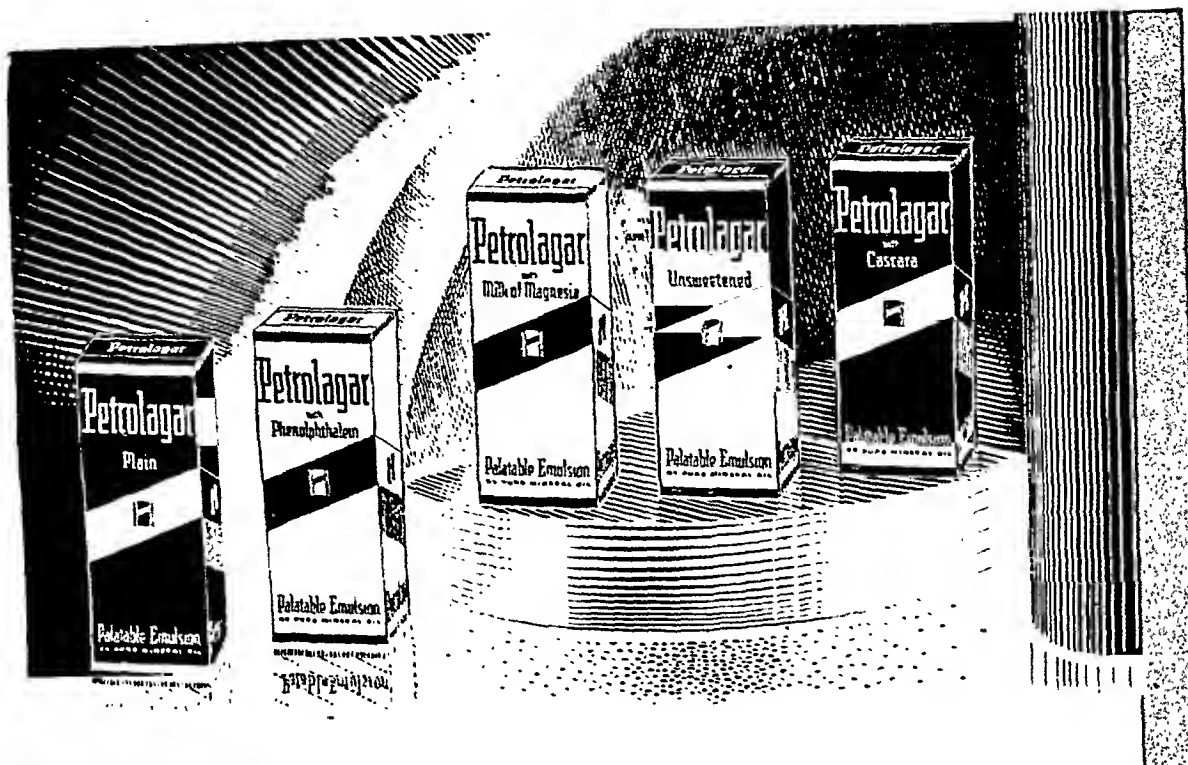
Naphco has a remedial effect quite beyond expectations, except to those physicians who have given it an exhaustive trial.

### JELLY of ALPHA NAPHCO in Capsules

In Amoebic Dysentery and in Amoebiasis without frank diarrhea, the use of Alpha Naphco in liquid or capsule form has a definite place in the armamentarium of the gastroenterologist,—it brings results as testified by a growing list of clinical investigators. These striking results may be due to the influence of the preparations upon the secondary invaders, whose importance is well recognized. In seasonal diarrheas, due to *B. dysenteriae*, or *B. welchii*, and in cases where the etiology cannot be readily discovered, Alpha Naphco therapy is winning a prominent place, both as an independent agent and as a most valuable adjunct to other forms of specific medication.

Exhaustive clinical and animal experiments have conclusively demonstrated the non-toxicity of the preparations... On receipt of your letter head or a page from your prescription book we shall be glad to send you supplies for clinical test and condensed reports.

**Carel Laboratories**  
Redondo Beach California



# HERE ARE THE 5 TYPES ★

THEY afford a range of laxative potency which will meet practically every requirement of successful bowel management. ● Petrolagar is a mechanical emulsion of pure liquid petrolatum (65% by volume) and agar-agar deliciously flavored and pleasant to take. ● It does not upset digestion, mixes easily with the intestinal content, acts as unabsorbable fluid and has less tendency to leakage.

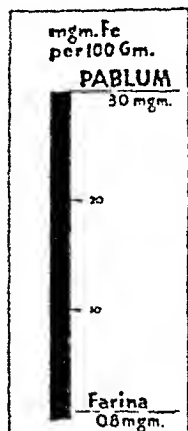


SAMPLES FREE ON REQUEST

**Petrolagar Laboratories, Inc., Chicago**

# For bland diet therapy, especially ULCER cases—PABLUM

**F**AR too often the bland diet prescribed for gastric ulcer, colitis, and similar gastro-intestinal disorders is a deficient diet. An analysis made by Troutt of ulcer diets used by 6 leading hospitals in different sections of the country showed them to be "well below the Sherman standard of 15 milligrams" in iron and low in the water-soluble vitamins. "Vitamin B would appear to be represented at a maintenance level in most cases," writes Troutt, "but the possible relation of vitamin B to gastro-intestinal function and appetite should make one pause before accepting a low standard."



Although Pablum has a low fiber content it is 37 times richer than farina in iron and in calcium, 4 times richer in phosphorus, and  $4\frac{1}{2}$  times richer in copper.

## Low in Fiber—High in Iron

Pablum is the only food rich in a wide variety of the necessary food factors that can be fed over long periods of time without danger of gastro-intestinal irritation. Its fiber content is only 0.9%. Yet Pablum contains 37 times more iron than farina and is an excellent source (+ + +) of vitamins B and G, in which farina is deficient. Supplying  $8\frac{1}{2}$  mgms. iron per ounce, Pablum is 8 times richer than spinach in iron.

## Rich in Vitamin B

The high vitamin B content of Pablum assumes new importance in light of recent laboratory studies showing that avitaminosis B predisposes to certain gastro-intestinal disorders. Apropos of this, Cowgill says, "Gastric ulcer is another disorder which can conceivably be related to vitamin B deficiency. Insofar as the treatment of this condition usually involves a marked restriction of diet the occurrence of at least a moderate shortage of this vitamin is by no means unlikely."

Requiring no further cooking, Pablum is especially valuable during the healing stage of ulcer when the patient is back at work but still requires frequent meals. Pablum can be prepared quickly and conveniently at the office or shop simply by adding milk or cream and salt and sugar to taste. Pablum has the added advantage that it can be prepared in many varied ways—in muffins, mush, puddings, junket, etc. Further, Pablum is so thoroughly cooked that its cereal-starch has been shown to be more quickly digested than that of farina, oatmeal, cornmeal, or whole wheat cooked four hours in a double boiler (studies *in vitro* by Ross and Burrill). In addition to the above advantages, Pablum is the only base-form cereal (except Mead's Cereal which is the uncooked form of Pablum).

Pablum (Mead's Cereal thoroughly pre-cooked) consists of wheatmeal, oatmeal, cornmeal, wheat embryo, alfalfa, yeast, beef bone, iron salt and sodium chloride. <sup>1,2</sup> Bibliography on request.

**MEAD JOHNSON & COMPANY - - Evansville, Indiana, U. S. A.**

Please enclose professional card when requesting samples of Mead Johnson products to cooperate in preventing their reaching unauthorized persons.

## EXICOL

**I**NDICATED in hepato-biliary disorders when dependable cholagogue and choleretic action is desired.

In prescribing Exicol you have the advantage of an effective therapeutic agent checked in the animal laboratory and clinically.

Exicol therapy is based on latest known and accepted physiologic principles governing the biliary apparatus.

**ACTION:** 1. It stimulates gall bladder evacuations (Cholagogue) and  
2. Increases bile flow from the liver (Choleretic).

**DOSE:** 2 capsules t.i.d.a.c.  
In boxes of 36 and 100.

Literature and samples on request

**Brooklyn Scientific Products Company, Inc.**

80 Fourth Ave. New York, N. Y.

## PROFESSIONAL STATIONERY

### Introductory Offer

500 Each  
Letter Heads,  $5\frac{1}{2} \times 8\frac{1}{2}$  } **\$3<sup>50</sup>** Prepaid  
Envelopes,  $3\frac{1}{2} \times 6\frac{1}{2}$

500 Each  
Statements,  $5\frac{1}{2} \times 5\frac{1}{4}$  } **\$3<sup>85</sup>** Prepaid  
Envelopes,  $3\frac{1}{2} \times 6\frac{1}{2}$

500 Each  
Letter Heads  
Statements &  
Envelopes } **\$5<sup>25</sup>** Prepaid

Stationery Printed on 20 lb. White  
Caslon Bond

(Remittance Must Accompany Order)  
10% Additional West of the Mississippi River  
SAMPLES SENT ON REQUEST

**MARVEL SALES CO.**  
360 No. Michigan Ave. Chicago, Ill.

Professional Stationery of Quality

# Sectional Index for Volume Two

## SECTION I—CLINICAL MEDICINE

|                                                                                                                                                                                                                     |         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Diarrhea, <i>John L. Kantor, M.D.</i> .....                                                                                                                                                                         | 1       |
| Constipation, <i>Henry James Spencer, A.M., M.D.</i> .....                                                                                                                                                          | 7       |
| The Weltmann Test in Diseases of the Liver, <i>Manfred Kraemer, M.D.</i> .....                                                                                                                                      | 14      |
| Diverticula of the Duodenum and Diabetes, <i>William B. Thorning, Jr., M.D., and Howard F. Root, M.D.</i> .....                                                                                                     | 17      |
| Vaccine Therapy in Ulcerative Colitis, <i>Sibrand Lups, M.D.</i> .....                                                                                                                                              | 65, 139 |
| Unrecognized "Strokes" and the Gastro-Enterologist, <i>Walter C. Alvarez, M.D.</i> .....                                                                                                                            | 90      |
| Liver Function in Hepatic and Extrahepatic Diseases, <i>G. K. Weaver, M.D.; T. L. Althausen, M.D.; G. R. Biskind, M.D., and Wm. J. Kerr, M.D.</i> .....                                                             | 93, 167 |
| Hepatoptosis, <i>Charles W. McClure, M.D.; Herman A. Osgood, M.D., and J. P. Bill, M.D.</i> .....                                                                                                                   | 161     |
| Intestinal Tuberculosis: A Clinical Roentgenological and Pathological Study of 2086 Patients Affected with Pulmonary Tuberculosis, <i>Emil Granet, A.B., M.D.</i> .....                                             | 209     |
| Stomach Lavage Microscopy as an Aid in the Diagnosis of Biliary Tract Disease, <i>Henry A. Rafsky, M.D., F.A.C.P.</i> .....                                                                                         | 214     |
| A Clinical Interpretation of Duodenal Diverticulum, <i>Herman H. Riecker, M.D.</i> .....                                                                                                                            | 217     |
| Recent Development in the Study of Oral Bacterial Flora, <i>Lloyd Arnold, M.D., and Carroll W. Stuart, D.D.S., M.D.</i> .....                                                                                       | 275     |
| Gastroscoy: Past, Present and Future, <i>Edwin Boros, M.D.</i> .....                                                                                                                                                | 280     |
| A New Tube for Anaesthetization of the Hypopharynx, <i>Rudolf Schindler, M.D.</i> .....                                                                                                                             | 281     |
| On the Etiology of Peptic Ulcer: An Analysis of 70 Ulcer Patients, <i>Samuel C. Robinson, M.D.</i> .....                                                                                                            | 333     |
| A Follow-Up of Ulcerative Colitis (Non-Specific), <i>Burrill B. Crohn, M.D., and Bernard D. Rosenak, M.D.</i> .....                                                                                                 | 343     |
| The Acutely Ill, Jaundiced Patient: A Report of Twenty-One Instances of Hepatic Icterus, Seven of Whom Had High Blood Nitrogen, <i>S. G. Meyers, M.D.; Osborne A. Brines, M.D., and Benjamin Juliar, M.D.</i> ..... | 346     |
| A Clinical Review of Giardiasis: Twenty-Two Cases Observed During Study of 572 Private Patients, <i>G. S. dePaula e Silva, M.D.</i> .....                                                                           | 350     |
| A Consideration of the Patient With Gastro-intestinal Complaints But Who is Without Evidences of Organic Pathology, <i>G. Alexander Young, M.D., and Richard H. Young, M.D.</i> .....                               | 353     |
| Non-Tuberculous Mesenteric Lymphadenitis in Childhood, <i>Louis H. Segar, M.D., and B. D. Rosenak, M.D.</i> .....                                                                                                   | 356     |
| A Philosophic, Clinical and Retrospective Discussion of Certain Major Problems in the Digestive Field, <i>Thomas R. Brown, M.D.</i> .....                                                                           | 391     |
| Migraine: A Common-Sense Approach, <i>Libby Pulsifer, M.D.</i> .....                                                                                                                                                | 397     |

|                                                                                                                                                                                                                                    |     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| The Validity of Fractional Gastric Analysis, <i>Frances A. Hellebrandt, M.D., and Elizabeth Brogdon, M.S.</i> .....                                                                                                                | 402 |
| Studies on the Relation of Non-Specific Ulcerative Colitis to Bacillary Dysentery (With Particular Reference to the Dysentery Bacteriophage) <i>A. Winkelstein, M.D., and C. Herschberger</i> .....                                | 408 |
| Acute Pancreatitis: A Clinical and Pathological Study, With Personal Observations, <i>Albert LeSage, M.D., F.R.C.P., and Jean R. A. LeSage, B.A., M.D.</i> .....                                                                   | 449 |
| Bacteriological Observations in Disease of the Biliary Tract: A Comparison of Operative Findings With Those of Non-Surgical Drainage of the Biliary Tract in 104 Cases, <i>Eilif Hansen, M.D., and Antony Yurevich, M.D.</i> ..... | 460 |
| Calculating the Diagnostic Value of Gastric Analysis: A Study in the Methodology of Diagnosis, <i>Frances R. Vanzant, M.D., and Walter C. Alvarez, M.D.</i> .....                                                                  | 466 |
| Gall Stones, <i>A. J. Delario, M.D.</i> .....                                                                                                                                                                                      | 511 |
| Abdominal Pain as a Misleading Symptom of Spinal Cord Lesions, <i>Everett D. Keifer, A.B., M.D.</i> .....                                                                                                                          | 520 |
| The Experimental Study of Visceral Disease, <i>Martin E. Rehfuess, M.D., and Guy M. Nelson, M.D.</i> .....                                                                                                                         | 593 |
| Psychogenic Factors in Ulcerative Colitis, <i>Arthur J. Sullivan, M.D.</i> .....                                                                                                                                                   | 651 |
| Gastroscoy With a Flexible Gastroscope; <i>Rudolf Schindler, M.D.</i> .....                                                                                                                                                        | 656 |
| Bacteriological Findings in Disease of the Biliary Tract: An Improved Method of Obtaining Cultures of Bile by Duodenal Drainage, <i>John Russell Twiss, M.D., and Charlotte H. Phillips, M.D.</i> .....                            | 663 |
| The Incidence and Biological Characteristics of the Hemolytic Bacillus Coli in the Intestinal Tract of Patients With Chronic Ulcerative Colitis, <i>Edith E. Nicholls, M.D.</i> .....                                              | 709 |
| The Takata-Ara Test of Liver Function, <i>Thomas B. Magath, M.D.</i> .....                                                                                                                                                         | 713 |
| The Hippuric Acid Test for Hepatic Function; Its Relation to Other Tests in General Use, <i>Albert M. Snell, M.D., and John E. Plunkett, M.D.</i> .....                                                                            | 716 |
| Phenolphthalein Studies: I. Colloidal Phenolphthalein, <i>Bernard Fantus, M.D., and J. M. Dyniewicz</i> .....                                                                                                                      | 721 |

## SECTION II—EXPERIMENTAL PHYSIOLOGY

|                                                                                                                                                      |     |
|------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Studies on the Neutralization of Gastric Acidity, <i>Robert Elman, M.D., and J. Wendell MacLeod, M.D.</i> .....                                      | 21  |
| Decompression of the Obstructed Biliary System of the Cat, <i>Harold L. Stewart, M.D., and Abraham Cantarow, M.D.</i> .....                          | 101 |
| The Parallel Concentration of Enzymes in the Pancreatic Juice, <i>Stewart G. Baxter, M.D., Ph.D.</i> .....                                           | 108 |
| Decompression of the Obstructed Biliary System in the Cat, <i>Abraham Cantarow, M.D.; Harold L. Stewart, M.D., and Stanley G. McCool, M.D.</i> ..... | 174 |

|                                                                                                                                                                                                                        |     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| The Mechanism of the Delay in Gastric Emptying Time Caused by Anoxemia, <i>George Crisler, Ph.D., M.D.; E. J. Van Liere, Ph.D., M.D., and I. A. Wiles, M.S.</i>                                                        | 221 |
| Quantitative Estimation of Enzyme Concentration in Duodenal Fluids: A Practical Clinical Method, <i>Charles W. Lueders, M.D.</i>                                                                                       | 224 |
| The Origin and Significance of the Blood Serum Enzymes, <i>Lathan A. Crandall, Jr., M.D., Ph.D.</i>                                                                                                                    | 230 |
| A Symposium Concerned With the Duodenal Factors in the Neutralization of Acid Chyme, <i>Frank C. Mann, M.D., and Jesse L. Bollman, M.D.</i>                                                                            | 284 |
| The Reaction of the Content of the Isolated Duodenum, <i>Pat R. Imes, M.D.</i>                                                                                                                                         | 285 |
| The Capacity of the Duodenum to Neutralize, Buffer and Dilute Acid, <i>G. Arnold Stevens, M.D.</i>                                                                                                                     | 288 |
| The Reaction of the Duodenal Content After Exclusion of Bile From the Duodenum, <i>Jerry W. McRoberts, M.D.</i>                                                                                                        | 293 |
| The Effect of Exclusion of the Pancreatic Secretion by Evulsion of the Pancreatic Ducts on the Reaction of the Duodenal Content, <i>M. Tischer Hoerner, M.D.</i>                                                       | 295 |
| The Effect of Exclusion of the Pancreatic Secretion by a Pancreatic Fistula on the Reaction of the Gastric, Duodenal and Jejunal Contents, <i>M. Tischer Hoerner, M.D.</i>                                             | 298 |
| The Buffer Capacity of the Pancreatic Juice, <i>M. Tischer Hoerner, M.D.</i>                                                                                                                                           | 300 |
| Peptic Ulcer Following Loss of Pancreatic Secretion Through a Fistula: An Experimental Study, <i>M. Tischer Hoerner, M.D.</i>                                                                                          | 302 |
| The Effect of Oxygen Inhalation on Gaseous Distention of the Stomach and the Small Intestine, <i>Jacob Fine, M.D.; John B. Sears, M.D., and Benjamin M. Banks, M.D.</i>                                                | 361 |
| The Pancreas and General Metabolism: A Physiological, Metabolic and Philosophical Concept of Nutritional Unity and Interdependence, <i>W. N. Boldyreff, M.D.</i>                                                       | 413 |
| The Auto Regulation of the Gastric Secretion, <i>J. J. Day, M.D., and D. R. Webster, M.D., Ph.D.</i>                                                                                                                   | 527 |
| The Cause of the Faulty Digestion in Dogs Without Stomachs, <i>Edward S. Emery, Jr., M.D.</i>                                                                                                                          | 599 |
| Experimental Studies in Gastric Physiology in Man: The Mechanism of Gastric Evacuation After Partial Gastrectomy as Demonstrated Roentgenologically, <i>Harry Shay, M.D., and J. Gerken-Cohen, M.D., M.Sc., (Med.)</i> | 608 |
| V. The Effects of Drugs on the Motility of Isolated Segments of the Intestine of Man, <i>J. Arnold Bergen, M.D., and John S. Guthrie, M.D.</i>                                                                         | 668 |
| Some Normal Variations in the Emptying-Time of the Human Stomach (Using a Carbohydrate Meal), <i>Edward J. Van Liere, Ph.D., M.D., and Carl K. Sleeth, A.B., B.S.</i>                                                  | 671 |
| The Influence of Some Organic and Inorganic Acids on the Motility of the Small Intestine, <i>N. M. Gray, M.D., M.Sc.</i>                                                                                               | 725 |

### SECTION III—NUTRITION

|                                                                                                                        |    |
|------------------------------------------------------------------------------------------------------------------------|----|
| Glycosuria and Lactosuria of Pregnant and of Lactating Women, <i>Henry J. Brock, M.D., and Roger S. Hubbard, Ph.D.</i> | 27 |
| Dry Natural Digestive Juices, <i>W. N. Boldyreff, M.D.</i>                                                             | 33 |

|                                                                                                                                                                                                                                                      |     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Milk, <i>Horace W. Soper, M.D.</i>                                                                                                                                                                                                                   | 113 |
| Clinical Evidence of Fifty So-Called Gastrointestinal Diseases Which Really are Caused by Food Allergy With Discussion of Their Treatment, <i>Josef S. Smul, M.D.</i>                                                                                | 178 |
| Insulin-Glucose Therapy in Heart Disease, <i>E. Sterling Nichol, M.D.</i>                                                                                                                                                                            | 236 |
| Acid-Base and Assimilability of Fruit Juices, <i>I. Newton Kugelmass, M.D.</i>                                                                                                                                                                       | 242 |
| A New Concept of Meniere's Disease and Its Response to Antiretentional Therapy, <i>Eugene Foldes, M.D.</i>                                                                                                                                           | 243 |
| Protection of Nutrition During the Use of "Elimination Diets," <i>Albert H. Rowe, M.D.</i>                                                                                                                                                           | 306 |
| The Role of Serum-Calcium Fractions in the Effect of Viosterol on the Bleeding Tendency in Jaundice, <i>J. S. Gray, M.S., and A. C. Ivy, M.D.</i>                                                                                                    | 368 |
| What Should be the Per Capita Per Day Milk Consumption of Our Population?, <i>Lloyd Arnold, M.D.</i>                                                                                                                                                 | 416 |
| A Year's Exclusive Meat Diet and Seven Years Later, <i>Clarence W. Lieb, A.M., M.D.</i>                                                                                                                                                              | 473 |
| Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes. IV. Block of the Reticulo-Endothelial System With Special Reference to the Kupffer Cell, <i>T. L. Althausen, M.D.; B. E. Blomquist, M.A., and E. F. Whedon, M.S.</i> | 532 |
| Studies on Crystalline Vitamin B <sub>1</sub> : Observations in Diabetes, <i>Martin G. Vorhaus, M.D.; Robert R. Williams, M.S., and Robert E. Waterman, B.S.</i>                                                                                     | 541 |
| Gastro-Intestinal Manifestations of Hyperinsulinism, <i>Scule Harris, M.D.</i>                                                                                                                                                                       | 557 |
| Present Conceptions of Calcium Metabolism, <i>David Landsborough Thomson</i>                                                                                                                                                                         | 614 |
| Blood Buffer Values in Mineral Deficiency, <i>I. Newton Kugelmass, M.D.</i>                                                                                                                                                                          | 730 |
| Statement, <i>Clarence W. Lieb, A.M., M.D.</i>                                                                                                                                                                                                       | 732 |

### SECTION IV—ROENTGENOLOGY

|                                                                                                                                                                          |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Caseade Stomach: A Review, <i>Roy Upham, M.D., F.A.C.S.</i>                                                                                                              | 38  |
| Dysphagia—Roentgenologically Considered, <i>L. S. Otell, M.D., and Fred O. Coe, M.D.</i>                                                                                 | 117 |
| Diverticular Sarcoma of the Stomach, <i>James T. Case, M.D., F.A.C.S.</i>                                                                                                | 185 |
| Carcinoma of the Body of the Pancreas: A Clinico-Roentgenologic Diagnosis, <i>Martin G. Vorhaus, M.D.</i>                                                                | 248 |
| Diverticulum of the Stomach, <i>Ellis B. Freilich, M.D.; Gerhard Danelius, M.D., and George C. Coe, M.D.</i>                                                             | 252 |
| Diaphragmatic Hernia: With a Report of Ten Cases of Oesophageal Orifice Hernia, <i>Katherine S. Andrews, M.D.</i>                                                        | 310 |
| Appendiceal Abscess: A Roentgenologic Consideration, With Especial Reference to the Diagnostic Difficulties and Its Differential Diagnosis, <i>Maurice Feldman, M.D.</i> | 373 |
| The Role of Vitamin B <sub>1</sub> in Tonus of the Large Intestine, <i>M. I. Sparks, M.D., and E. N. Collins, M.D.</i>                                                   | 618 |



## SECTION V—THERAPEUTICS

|                                                                                                                                                                                                                                                                                     |     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Therapy of Non-Malignant Biliary Tract Lesions, <i>Allen O. Whipple, M.D.</i> . . . . .                                                                                                                                                                                             | 44  |
| The Use of Duodenal Extract as an Adjuvant in the Treatment of Benign Peptic Lesions: Report of Eight Cases, <i>Andrew B. Rivers, M.D.</i> . . . .                                                                                                                                  | 189 |
| Treatment of Hemorrhage Caused by Peptic Ulcer, <i>G. A. Hendon, M.D.</i> . . . . .                                                                                                                                                                                                 | 255 |
| A Symposium on Management of Oesophagitis, <i>Walter A. Bastedo, M.D.; Julius Friedenwald, M.D., and Horace W. Soper, M.D.</i> . . . . .                                                                                                                                            | 379 |
| The Treatment of Food Allergy and Indigestion of Pancreatic Origin With Pancreatic Enzymes, <i>Anton W. Oelgoetz, M.D.; Paul A. Oelgoetz, B.A., and Juanita Wittekind, R.N.</i> . . . . .                                                                                           | 422 |
| Histidine in the Treatment of Peptic Ulcer: A Preliminary Report, <i>John T. Eads, M.D.</i> . . . .                                                                                                                                                                                 | 426 |
| Gastro-Intestinal Diets, Diet Manual, Mount Sinai Hospital . . . . .                                                                                                                                                                                                                | 476 |
| The Treatment of Amoebiasis With Iodoxyquinolin Sulphonic Acid, <i>F. W. O'Connor, M.R.C.S., and C. R. Hulse</i> . . . . .                                                                                                                                                          | 568 |
| Colon Bacillus Vaccine Therapy as Related to Chronic Functional Diarrhea, Chronic Headache, Chronic "Toxic Vertigo" and "Unstable" Colon (Non-Ulcerative Colitis), <i>John G. Mateer, M.D.; James I. Baltz, M.D.; James Fitzgerald, M.D., and Harris L. Woodburne, M.D.</i> . . . . | 621 |
| A New Technique for the Continuous Control of Acidity in Peptic Ulcer by the Aluminum Hydroxide Drip, <i>E. E. Woldman, M.D., and V. C. Rowland, M.D.</i> . . . . .                                                                                                                 | 738 |
| Therapy of Peptic Ulcer: Conservative Versus Radical, <i>Ernest H. Gaither, M.D.</i> . . . .                                                                                                                                                                                        | 736 |

## SECTION VI—ABDOMINAL SURGERY

|                                                                                                                                        |     |
|----------------------------------------------------------------------------------------------------------------------------------------|-----|
| Diagnosis and Treatment of Amebic Abscess of the Liver, <i>Alton Ochsner, M. D., and Michael De-Bakey, M.D.</i> . . . . .              | 47  |
| Factors Pertinent to the Reduction of the Mortality in Cholecystectomy, <i>Moses Behrend, M.D. F.A.C.S.</i> . . . . .                  | 258 |
| The Use of Metal Clips in Gastrointestinal Anastomosis, <i>Ralph B. Bettman, M.D., and Leo M. Zimmerman, M.D.</i> . . . . .            | 318 |
| Bleeding Gastric and Duodenal Ulcers, <i>A. Philip MacGuire, A.B., M.D., F.A.C.S.</i> . . . . .                                        | 431 |
| Gastro-Intestinal Manifestations Accompanying Diseases in the Upper Urinary Tract, <i>Benjamin S. Abeshouse, Ph.B., M.D.</i> . . . . . | 477 |
| Aseptic Electrosurgical Enterostomy: A New Method, <i>Lester R. Whitaker, M.D.</i> . . . .                                             | 630 |
| Experiences With Postoperative Jejunal Ulcers and Gastrojejunal Colic Fistula, <i>Frank H. Lahey, M.D.</i> . . . .                     | 673 |

## SECTION VII—SURGERY OF THE LOWER COLON AND RECTUM

|                                                                                                               |     |
|---------------------------------------------------------------------------------------------------------------|-----|
| Pruritis Ani: A New Treatment, <i>Nathan J. Simmons, M.D.</i> . . . . .                                       | 53  |
| The Modern Proctologic Clinic, <i>Martin J. Synnott, M.A., M.D., F.A.C.P.</i> . . . . .                       | 196 |
| The Specificity of the Frei Test in Lymphopathia Venerea, <i>Harry E. Bacon, B.S., M.D., F.A.C.S.</i> . . . . | 570 |

|                                                                                                                                                     |          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| The Haemorrhoidal Lesion: Its Radical Cure by Submucous Injection With or Without the Ligation Operation, <i>E. A. Daniels, M.Sc., M.D.</i> . . . . | 631      |
| Traumas Resulting From Sigmoid Manipulation, <i>Burrill B. Crohn, M.D., and Bernard D. Rosenak, M.D.</i> . . . . .                                  | 678      |
| Annual Abstracts of Proctologic Literature, <i>Clement L. Martin, M.D.</i> . . . . .                                                                | 682, 746 |
| Lymphopathia Venerea: A Clinical Survey, <i>Collier F. Martin, M.D., F.A.C.S.</i> . . . . .                                                         | 741      |
| Recto-Urethral Fistula: An Operation For Its Cure, <i>Cecil D. Gaston, M.D., F.A.C.S., and A. B. Lee, M.D.</i> . . . . .                            | 744      |

## SECTION VIII—EDITORIAL

|                                                                                                                                                                                   |     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| General Principles Involved in the Diagnosis of Gastro-Intestinal Disease, <i>Harlow Brooks, M.D.</i> . . . .                                                                     | 56  |
| Enterogastrone, <i>A. C. Ivy, M.D.</i> . . . . .                                                                                                                                  | 58  |
| The Concept of "Combined Acidity" in Gastric Juice Studies, <i>Franklin Hollander, Ph.D.</i> . . . .                                                                              | 127 |
| Is the Public Being Stampeded in Regard to Vitamins?, <i>Walter C. Alvarez, M.D.</i> . . . .                                                                                      | 128 |
| Dr. Sibrand Lups' Monograph Concerning "Chronic Ulcerative Colitis" and an Appreciation of Its Translation Into English by Dr. Abel J. Baker, <i>Frank Smithies, M.D.</i> . . . . | 130 |
| The Common Pathogenesis of Terminal Ileitis, Idiopathic Ulcerative Colitis and Bacillary Dysentery, <i>Walter A. Bastedo, M.D.</i> . . . .                                        | 201 |
| New York City Active for the American Board of Gastro-enterology, <i>Anthony Bassler, M.D.</i> . . . .                                                                            | 201 |
| Advertisements Should Be Read, <i>Frank Smithies, M.D.</i> . . . .                                                                                                                | 261 |
| Abandoning Free Reprints, <i>Frank Smithies, M.D.</i> . . . .                                                                                                                     | 262 |
| Passage of Native Proteins Through the Normal Gastro-Intestinal Wall, <i>Bret Ratner, M.D.</i> . . . .                                                                            | 324 |
| Brevity, <i>Frank Smithies, M.D.</i> . . . . .                                                                                                                                    | 325 |
| Greetings to the Spanish Journal of Diseases of the Digestive Apparatus and of Nutrition, <i>The Editorial Council</i> . . . . .                                                  | 380 |
| American Board of Gastro-enterology, <i>A. F. R. Andresen, M.D.</i> . . . .                                                                                                       | 380 |
| Report of the President, <i>A. F. R. Andresen, M.D.</i> . . . .                                                                                                                   | 380 |
| Report From American Board of Gastro-enterology to the Section of Gastro-enterology and Proctology of the American Medical Association . . . . .                                  | 381 |
| Cholesterol, <i>Horace W. Soper, M.D.</i> . . . . .                                                                                                                               | 381 |
| On An Adequate Conception of the Etiology and the Significance of Peptic Ulcer (Gastric and Duodenal), <i>Frank Smithies, M.D.</i> . . . .                                        | 437 |
| President's Address, <i>B. B. Vincent Lyon, M.D.</i> . . . .                                                                                                                      | 495 |
| The Diagnosis of Gastritis, <i>George Eusterman, M.D.</i> . . . .                                                                                                                 | 575 |
| On the Proposed "Institute for Gastro-Enterological Research," <i>Frank Smithies, M.D.</i> . . . .                                                                                | 634 |
| Proctology, A Speciality, and Its Influence Upon This Journal's Publication Policy, <i>Frank Smithies, M.D.</i> . . . .                                                           | 635 |
| The Great Value of Some Physiological Observations on Man, <i>Walter C. Alvarez, M.D.</i> . . . .                                                                                 | 683 |
| The Etiology of Peptic Ulcer: A Review of One Theory, <i>Maurice B. Bonta, M.D.</i> . . . .                                                                                       | 683 |

|                                                                                        |     |
|----------------------------------------------------------------------------------------|-----|
| The Journal's Second Birthday, <i>Braumont S. Cornell, M.D., F.A.C.S.</i>              | 747 |
| Regarding the "House" Page and Certain Editorial Problems, <i>Frank Smithies, M.D.</i> | 747 |

## SECTION IX—BOOK REVIEWS

|                                                                                                                                                                                 |     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| <i>Treatment by Diet</i> by <i>Clifford J. Barborka</i> . Reviewed by <i>Frank Smithies</i>                                                                                     | 59  |
| <i>Cirugia Gastrica</i> , Vol. I by <i>M. Corachan</i> . Reviewed by <i>Walter C. Alvarez</i>                                                                                   | 61  |
| <i>Food for the Diabetic</i> by <i>Mary P. Huddleson</i> , Consulting Dietitian. Reviewed by <i>Clifford J. Barborka</i>                                                        | 61  |
| <i>The Physiology of the Gall Bladder</i> by <i>A. C. Ivy</i> . Reviewed by <i>Dwight L. Wilbur</i>                                                                             | 131 |
| <i>The Automatic Diseases or the Rheumatic Syndrome</i> by <i>T. M. Rivera</i> . Reviewed by <i>R. M. Wilder</i>                                                                | 133 |
| <i>Diet Manucl</i> , St. Mary's Hospital by <i>Sister Mary Victor</i> . Reviewed by <i>Frank Smithies</i>                                                                       | 202 |
| <i>Physiology in Modern Medicine</i> by <i>J. J. R. Macleod</i> . Reviewed by <i>Frederic T. Jung</i>                                                                           | 262 |
| <i>Emotions and Bodily Changes</i> by <i>H. Flanders Dunbar</i> . Reviewed by <i>Beaumont S. Cornell</i>                                                                        | 263 |
| <i>Body Mechanics in the Study and Treatment of Disease</i> by <i>J. E. Goldthwait, L. T. Brown, L. T. Swain, and J. G. Kuhns</i> . Reviewed by <i>Franklin W. White</i>        | 326 |
| <i>Methods of Treatment</i> by <i>Logan Clendenen</i> . Reviewed by <i>Leon Bloch</i>                                                                                           | 326 |
| <i>Radiologie Clinique Du Tube Digestif</i> , Publiee Sous La Direction Se Mm. by <i>Pierre Duxal, Jean-Charles Rour, and Henri Beclerc</i> . Reviewed by <i>Frank Smithies</i> | 382 |
| <i>Textbook of Biochemistry</i> by <i>Harrow and Sherwin</i> . Reviewed by <i>A. C. Ivy</i>                                                                                     | 384 |
| <i>The Patient and the Weather</i> , Vol. II, <i>Anatomic Dysintegration</i> by <i>William F. Peterson and Margaret E. Milliken</i> . Reviewed by <i>Walter C. Alvarez</i>      | 440 |
| <i>Preview of Dr. B. B. Vincent Lyon's "Atlas"</i> by <i>Frank Smithies</i>                                                                                                     | 441 |
| <i>Traite De Gastrosomie Et De Pathologie Endoscopique De L'Estomac</i> by <i>Francois Moutier</i> . Reviewed by <i>Martin E. Rehfuess</i>                                      | 576 |
| <i>An Atlas on Biliary Drainage Microscopy</i> by <i>B. B. Vincent Lyon</i> . Reviewed by <i>Frank Smithies</i>                                                                 | 578 |
| <i>Vegetables and Their Significance in the Physiology of Digestion</i> by <i>N. T. Leporsky</i> . Reviewed by <i>George W. Stavrakj</i>                                        | 638 |
| <i>Child Psychiatry</i> by <i>Leo Kanner</i> . Reviewed by <i>Frank Smithies</i>                                                                                                | 639 |
| <i>The Management of Colitis</i> by <i>J. Arnold Bagen</i> . Reviewed by <i>V. C. Rowland</i>                                                                                   | 685 |
| <i>Aids in Diminishing Operative Risk</i> by <i>Depuy de Frenelle</i> . Reviewed by <i>Pierre Smith and Thomas Farmer</i>                                                       | 749 |
| <i>Dietetics for the Clinician: Second Edition</i> by <i>Milton Arlander Bridges</i> . Reviewed by <i>Clifford J. Barborka</i>                                                  | 750 |

## SECTION X—AFTER "HOURS"

|                                                                                                                                                                      |     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| <i>An Exhibition of Books Illustrating the Progress of Gastroenterology Shown at the Graduate Fortnight</i> , <i>Burrill B. Crohn, M.D., and B. D. Rosenak, M.D.</i> | 264 |
| <i>Members of the Journal's Editorial Council Receive High Honors</i> , Anonymous                                                                                    | 499 |
| <i>Some Social and Medical Impressions of Moscow</i> , <i>Charles Gordon Heyd, B.A., M.D., F.A.C.S.</i>                                                              | 686 |

|                                                                                                                             |     |
|-----------------------------------------------------------------------------------------------------------------------------|-----|
| <i>Charles Gordon Heyd, B.A., M.D., F.A.C.S.</i>                                                                            | 686 |
| <i>The Fifteenth International Physiological Congress, Leningrad and Moseow, August 8-18, 1935</i> , <i>A. C. Ivy, M.D.</i> | 692 |
| <i>Johann Gregor Mendel, J. Duffy Hancock, M.S., M.D., F.A.C.S.</i>                                                         | 750 |

## SECTION XI—SOCIETIES, PROGRAMS AND PROCEEDINGS

|                                                                                                                                 |     |
|---------------------------------------------------------------------------------------------------------------------------------|-----|
| <i>Program of the American Gastro-Enterological Association</i>                                                                 | 133 |
| <i>Final Program of the Thirty-Eighth Annual Meeting of the American Gastro-Enterological Association</i>                       | 203 |
| <i>Changes in Membership, Committees, Etc.</i> , <i>Russell S. Bolcs, M.D., Sec'y</i>                                           | 385 |
| <i>In Memoriam: Albert Bernheim, David Reisman</i>                                                                              | 502 |
| <i>Report on the First International Congress of Gastro-Enterology Held at Brussels, Belgium</i> , <i>Anthony Bassler, M.D.</i> | 581 |
| <i>Delegates on the Part of the United States to the First International Congress of Gastro-Enterology</i>                      | 583 |
| <i>Report on the Annual Session of the American Proctologic Society</i> , <i>Curtice Rosser, M.D.</i>                           | 584 |
| <i>Annual Session of the American College of Physicians</i> , <i>E. R. Loveland, Executive Secretary</i>                        | 755 |

## SECTION XII—"THE CLINIC"

|                                                                                                                                                        |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| <i>Traumatic Duodenal Uleer in a 10 Year Old Boy</i> , <i>Jack Witherspoon, M.D.</i>                                                                   | 135 |
| <i>An Unusual Case of Primary Actinomyces Involving the Mesentery of the Small Intestine</i> , <i>C. J. Tidmarsh, M.A., M.D., F.R.C.P.(C)</i>          | 205 |
| <i>Incomplete Intestinal Obstruction Due to Shortened Ligament of Treitz</i> , <i>Joseph Stein, M.D.</i>                                               | 208 |
| <i>Gastrie Uleer Following Duodenal Uleer With Obstruction; Report of a Case</i> , <i>Fred R. Harper, M.D.</i>                                         | 271 |
| <i>An Instance of Marked Abdominal Distention With the Probable Etiologic Factors Being Abnormal Endocrine Function</i> , <i>George B. Dorff, M.D.</i> | 328 |
| <i>A Case of Gastrie Polyposis</i> , <i>A. C. van Ravensway, M.D.</i>                                                                                  | 386 |
| <i>Non-Tropical Sprue: Report of a Case</i> , <i>John A. Reed, A.B., M.D.</i>                                                                          | 388 |
| <i>Typical and Atypical Terminal Ileitis</i> , <i>A. Galambos, M.D., and W. Mittelmann, M.D.</i>                                                       | 442 |
| <i>Insulin-Glucose Therapy in Coronary Thrombosis</i> , <i>Gerald J. Kohne, M.D.</i>                                                                   | 447 |
| <i>Bilateral Massive Suprarenal Hemorrhage in An Instance of Hyperfunction of the Suprarenal Cortex</i> , <i>Frank R. Finnegan, M.D.</i>               | 504 |
| <i>Unusual Causes for Symptoms of Biliary Tract Disease, With Case Reports</i> , <i>J. W. Thompson, M.D., F.A.C.S.</i>                                 | 588 |
| <i>Large Epiphrenic Diverticulum of the Esophagus</i> , <i>B. D. Rosenak, M.D.</i>                                                                     | 642 |
| <i>A Case of Noma (Cancrum Oris) Complicating Non-Specific Ulcerative Colitis</i> , <i>Joseph S. Diamond, M.D.</i>                                     | 698 |
| <i>Spontaneous Gastro-Colic Fistula</i> , <i>Milton R. Louria, M.D., and Emil Rothstein, M.D.</i>                                                      | 756 |
| <i>Urogenital Symptoms Referable to Intra-Abdominal Disease</i> , <i>Charles Gordon Heyd, B.A., M.D., F.A.C.S.</i>                                     | 758 |

# Author Index for Volume Two

## A

|                       |                            |
|-----------------------|----------------------------|
| Abeshouse, B. S.      | 477                        |
| Althausen, T. L.      | 93, 167, 532               |
| Alvarez, Walter C.    | 61, 90, 128, 440, 466, 683 |
| Andresen, A. F. R.    | 380                        |
| Andrews, Katherine S. | 310                        |
| Arnold, Lloyd         | 275, 416                   |

## B

|                       |          |
|-----------------------|----------|
| Bacon, Harry E.       | 570      |
| Baltz, James I.       | 621      |
| Barborka, Clifford J. | 61, 750  |
| Bargen, J. Arnold     | 668      |
| Bassler, Anthony      | 201, 581 |
| Bastedo, Walter A.    | 201, 379 |
| Baxter, Stewart G.    | 108      |
| Behrend, Moses        | 258      |
| Bettman, Ralph B.     | 318      |
| Bill, J. P.           | 161      |
| Biskind, G. R.        | 93, 167  |
| Bloch, Leon           | 326      |
| Blomquist, B. E.      | 532      |
| Boldyreff, W. N.      | 33, 413  |
| Boles, Russell S.     | 385      |
| Bollman, Jesse L.     | 284      |
| Bonta, Maurice B.     | 683      |
| Boros, Edwin          | 280      |
| Brines, Osborne A.    | 346      |
| Brock, Henry J.       | 27       |
| Brogdon, Elizabeth    | 402      |
| Brooks, Harlow        | 56       |
| Brown, Thomas R.      | 391      |

## C

|                          |               |
|--------------------------|---------------|
| Cantarow, Abraham        | 101, 174      |
| Case, James T.           | 185           |
| Coe, Fred O.             | 117           |
| Coe, George C.           | 252           |
| Collins, E. N.           | 618           |
| Cornell, Beaumont S.     | 263, 747      |
| Crandell, Lathan A., Jr. | 230           |
| Crisler, George          | 221           |
| Crohn, Burrill B.        | 271, 343, 678 |

## D

|                    |          |
|--------------------|----------|
| Danielius, Gerhard | 252      |
| Daniels, E. A.     | 631, 724 |
| Day, J. J.         | 527      |
| DeBakey, Michael   | 47       |
| Delario, A. J.     | 511      |
| Diamond, Joseph S. | 698      |
| Dorff, George B.   | 328      |
| Dyniewicz, J. M.   | 721      |

## E

|                       |     |
|-----------------------|-----|
| Eads, John T.         | 426 |
| Elman, Robert         | 21  |
| Emery, Edward S., Jr. | 599 |
| Eusterman, George     | 575 |

## F

|                     |     |
|---------------------|-----|
| Fantus, Bernard     | 721 |
| Farmer, Thomas      | 749 |
| Feldman, Maurice    | 373 |
| Fine, Jacob         | 361 |
| Finnegan, Frank R.  | 504 |
| Fitzgerald, James   | 621 |
| Foldes, Eugene      | 243 |
| Freilich, Ellis B.  | 252 |
| Friedenwald, Julius | 379 |

## G

|                    |     |
|--------------------|-----|
| Gabor, M. E.       | 724 |
| Gaither, Ernest H. | 736 |
| Galambos, A.       | 442 |
| Gaston, Cecil D.   | 744 |
| Gershon-Cohen, J.  | 608 |
| Granet, Emil       | 209 |
| Gray, J. S.        | 368 |
| Gray, N. M.        | 725 |
| Guthrie, John S.   | 668 |

## H

|                         |                    |
|-------------------------|--------------------|
| Hancock, J. Duffy       | 750                |
| Hanks, Benjamin M.      | 361                |
| Hanssen, Eilif          | 460                |
| Harper, Fred R.         | 271                |
| Harris, Seale           | 557                |
| Hellebrandt, Frances A. | 402                |
| Hendon, G. A.           | 255                |
| Herschberger, C.        | 411                |
| Heyd, Charles Gordon    | 686, 758           |
| Hoerner, M. Tischer     | 295, 298, 300, 302 |
| Hollander, Franklin     | 127                |
| Hubbard, Roger S.       | 27                 |
| Hulse, C. R.            | 568                |

## I

|              |                        |
|--------------|------------------------|
| Imes, Pat R. | 285                    |
| Ivy, A. C.   | 58, 131, 368, 384, 692 |

## J

|                   |     |
|-------------------|-----|
| Juliar, Benjamin  | 346 |
| Jung, Frederic T. | 263 |

## K

|                      |          |
|----------------------|----------|
| Kantor, John L.      | 1        |
| Keifer, Everett D.   | 520      |
| Kerr, Wm. J.         | 93, 167  |
| Kohne, Gerald J.     | 447      |
| Kraemer, Manfred     | 14       |
| Kugelmass, I. Newton | 242, 730 |

## L

|                     |          |
|---------------------|----------|
| Lahey, Frank H.     | 673      |
| Lee, A. B.          | 744      |
| LeSage, Albert      | 449      |
| LeSage, Jean R. A.  | 449      |
| Lieb, Clarence W.   | 473, 732 |
| Louria, Milton R.   | 756      |
| Loveland, E. R.     | 755      |
| Lueders, Charles W. | 224      |
| Lups, Sibrand       | 65, 139  |
| Lyon, B. B. Vincent | 495      |

## M

|                     |          |
|---------------------|----------|
| McClure, Charles W. | 161      |
| McCool, Stanley G.  | 174      |
| McRoberts, Jerry W. | 293      |
| MacGuire, A. Philip | 431      |
| MacLeod, J. Wendell | 21       |
| Magath, Thomas B.   | 713      |
| Mann, Frank C.      | 284      |
| Martin, Clement L.  | 682, 746 |
| Martin, Collier F.  | 741      |
| Mateer, John G.     | 621      |
| Meyers, S. G.       | 346      |
| Mittelmann, W.      | 442      |

## N

|                     |     |
|---------------------|-----|
| Nelson, Guy M.      | 593 |
| Nichol, E. Sterling | 236 |
| Nicholls, Edith E.  | 709 |

|                         |                                                       |                             |          |          |  |
|-------------------------|-------------------------------------------------------|-----------------------------|----------|----------|--|
| <b>O</b>                |                                                       |                             |          |          |  |
| O'Connor, F. W.         | 568                                                   | Stavraky, George W.         | 638      |          |  |
| Oehsner, Alton          | 47                                                    | Stein, Joseph               | 208      |          |  |
| Oelgoetz, Anton W.      | 422                                                   | Stevens, G. Arnold          | 288      |          |  |
| Oelgoetz, Paul A.       | 422                                                   | Stewart, Harold L.          | 101, 174 |          |  |
| Osgood, Herman A.       | 161                                                   | Stuart, Carroll W.          | 275      |          |  |
| Otell, L. S.            | 117                                                   | Sullivan, Arthur J.         | 651      |          |  |
|                         |                                                       | Synnott, Martin J.          | 196      |          |  |
| <b>P</b>                |                                                       |                             |          | <b>T</b> |  |
| Phillips, Charlotte H.  | 667                                                   | Thompson, J. W.             | 588      |          |  |
| Plunkett, John E.       | 716                                                   | Thomson, David Landsborough | 614      |          |  |
| Pulsifer, Libby         | 397                                                   | Thorning, Wm. B.            | 17       |          |  |
|                         |                                                       | Tidmarsh, C. J.             | 206      |          |  |
| <b>R</b>                |                                                       | Twiss, John R.              | 667      |          |  |
| Rafsky, Henry A.        | 214                                                   |                             |          | <b>U</b> |  |
| Ratner, Bret            | 324                                                   | Upham, Roy                  | 38       |          |  |
| Ravenswaay, A. C. van   | 386                                                   |                             |          | <b>V</b> |  |
| Reed, John A.           | 388                                                   | Van Liere, E. J.            | 221, 671 |          |  |
| Rehfuss, Martin E.      | 576, 593                                              | Vanzant, Frances R.         | 466      |          |  |
| Reisman, David          | 502                                                   | Victor, Sister Mary         | 202      |          |  |
| Riecker, Herman H.      | 217                                                   | Vorhaus, Martin G.          | 248, 541 |          |  |
| Rivers, Andrew B.       | 189                                                   |                             |          | <b>W</b> |  |
| Rivers, T. M.           | 133                                                   | Waterman, Robert E.         | 557      |          |  |
| Robinson, Samuel C.     | 333                                                   | Webster, D. R.              | 527      |          |  |
| Root, Howard F.         | 17                                                    | Wever, G. K.                | 93, 167  |          |  |
| Rosenak, B. D.          | 264, 343, 356, 642, 678                               | Whedon, E. F.               | 532      |          |  |
| Rosser, Curtice         | 584                                                   | Whipple, Allen O.           | 44       |          |  |
| Rothstein, Emil         | 756                                                   | Whitaker, Lester R.         | 630      |          |  |
| Rowe, Albert H.         | 306                                                   | White, Franklin W.          | 326      |          |  |
| Rowland, V. G.          | 685, 733                                              | Wilbur, Dwight L.           | 131      |          |  |
|                         |                                                       | Wilder, R. M.               | 133      |          |  |
| <b>S</b>                |                                                       | Wiles, I. A.                | 221      |          |  |
| Schindler, Rudolf       | 281, 656                                              | Williams, Robert R.         | 541      |          |  |
| Sears, John B.          | 361                                                   | Winkelstein, A.             | 411      |          |  |
| Segar, Louis H.         | 356                                                   | Witherspoon, Jack           | 135      |          |  |
| Shay, Harry             | 608                                                   | Wittekind, Juanita          | 422      |          |  |
| Silva, G. S. de Paula e | 350                                                   | Woldman, E. E.              | 733      |          |  |
| Simmons, Nathan J.      | 53                                                    | Woodburne, Harris L.        | 621      |          |  |
| Sleeth, Carl K.         | 671                                                   |                             |          | <b>Y</b> |  |
| Smith, Pierre           | 749                                                   | Young, G. Alexander         | 353      |          |  |
| Smithies, Frank         | 59, 130, 202,                                         | Young, Richard H.           | 353      |          |  |
|                         | 261, 262, 325, 382, 437, 441, 578, 634, 635, 639, 747 | Yurevich, Antony            | 460      |          |  |
| Smul, Josef S.          | 178                                                   |                             |          | <b>Z</b> |  |
| Snell, Albert M.        | 716                                                   | Zimmerman, Leo M.           | 318      |          |  |
| Soper, Horace W.        | 113, 379                                              |                             |          |          |  |
| Sparks, M. I.           | 618                                                   |                             |          |          |  |
| Spencer, Henry J.       | 7                                                     |                             |          |          |  |

## General Index for Volume Two

|                                |     |                               |     |
|--------------------------------|-----|-------------------------------|-----|
| Abdomen, distention of         | 328 | Analysis, gastric             | 402 |
| Abscess, appendiceal           | 373 | value of                      | 466 |
| of liver, amebic               | 47  | Anastomosis, gastrointestinal | 318 |
| Acetocholine                   | 669 | Anastomosis intestinal        | 585 |
| Achalasia                      | 118 | Anemia, liver function in     | 97  |
| Acid-base value of fruit juice | 242 | macrocytic in cirrhosis       | 100 |
| Acid hydrochloric              | 394 | splenic                       | 717 |
| Acidity, combined              | 127 | ulcerative colitis in         | 67  |
| gastric, neutralization of     | 21  | Anoxemia, and gastric delay   | 217 |
| Actinomycosis, mesenteric      | 205 | Anus, melano-epithelioma of   | 327 |
| Agranulocytosis                | 682 | Anus, pruritis                | 53  |
| Alkalosis, kidneys in          | 309 | Anxiety, and peptic ulcer     | 672 |
| Aluminum hydroxide             | 723 | Apoplexy, unrecognized        | 90  |
| Amebiasis                      | 746 | Appendicitis, acute           | 51  |
| chronic                        | 63  | gastric bleeding in           | 62  |
| treatment of                   | 568 | Appendix                      | 395 |
| Amebic abscess of liver        | 47  | abscess of                    | 373 |
| Amylase, blood                 | 177 | perforated                    | 52  |

|                                          |                        |
|------------------------------------------|------------------------|
| Arteriosclerosis, experimental           | 696                    |
| Arthritis, diet in                       | 116, 308               |
| Atresia, of esophagus                    | 122                    |
| B. Coli in biliary tract                 | 460                    |
| B. Coli infections                       | 593                    |
| vaccine therapy                          | 621                    |
| B. typhosis, in biliary tract            | 460                    |
| B. Welchii, in biliary tract             | 460                    |
| Bacillus, coli, hemolytic                | 709                    |
| Bacteria, effect on stomach              | 367                    |
| Bacteriology, in biliary tract           | 460                    |
| in biliary tract disease                 | 663                    |
| of milk                                  | 115                    |
| post-mortem                              | 111                    |
| Bacteriophage, of dysentery              | 408                    |
| Bile, cultures of                        | 663                    |
| Bile Dust, common                        | 629                    |
| Biliary stasis, experimental             | 508                    |
| Biliary system, experimental obstruction | 174                    |
| Biliary tract disease                    | 460                    |
| causes                                   | 588                    |
| Bleeding, in ulcer peptic                | 431                    |
| Blood serum, enzymes in                  | 230                    |
| Brucella abortus                         | 309                    |
| Buffer values of blood                   | 730                    |
| Calcium bilirubinate                     | 216                    |
| deficiency                               | 370                    |
| metabolism of                            | 615                    |
| Cancer                                   | 393                    |
| gastric                                  | 649                    |
| of cardia                                | 42                     |
| of esophagus                             | 43                     |
| rectal                                   | 327                    |
| Cancrum oris                             | 698                    |
| Carbohydrate, and gastric motility       | 671                    |
| Carbonate, crystals                      | 215                    |
| Carcinoma, esophagus                     | 667                    |
| gastric                                  | 501, 641               |
| hepatic                                  | 95                     |
| of pancreas                              | 248                    |
| rectosigmoid                             | 195                    |
| Cardiospasm                              | 118                    |
| Cascade stomach                          | 38                     |
| Catarrh, in ulcerative colitis           | 71                     |
| Cecum, carcinoma of                      | 52                     |
| Chemistry of gall stones                 | 511                    |
| Cholangitis                              | 719                    |
| Cholecystectomy, mortality in            | 259                    |
| without stone                            | 677                    |
| Cholecystitis, bacteriology of           | 283                    |
| chronic                                  | 97                     |
| Cholesterol                              | 381                    |
| crystals                                 | 215                    |
| Chyme, neutralization of                 | 284                    |
| Cirrhosis, biliary                       | 717                    |
| experimental                             | 173                    |
| Clinic, modern proctologic               | 196                    |
| Clips, metal                             | 318                    |
| Colitis                                  | 396                    |
| management of                            | 685                    |
| ulcerative                               | 65, 135, 213, 309, 343 |
| ulcerative, B. Coli in                   | 709                    |
| ulcerative, cultural methods in          | 157                    |
| ulcerative and dysentery                 | 408                    |
| ulcerative and noma                      | 698                    |
| ulcerative, psychogenic factors          | 651                    |
| Colloidal phenolphthalein                | 721                    |
| Colon, absorption from                   | 435                    |
| cancer of                                | 696                    |
| carcinoma of                             | 327                    |
| diverticulitis of                        | 254                    |
| spastic                                  | 260                    |
| unstable                                 | 625                    |

|                                       |          |
|---------------------------------------|----------|
| Constipation                          | 7        |
| spastic                               | 625      |
| treatment                             | 85       |
| Coronary occlusion                    | 436      |
| Defecation, call to                   | 9        |
| nervous control                       | 672      |
| Deficiency, calcium                   | 370      |
| states                                | 309      |
| vitamin, experimental                 | 475      |
| Dextrose, absorption of               | 247      |
| Diabetes, and diverticula of duodenum | 17       |
| and vitamin B (1)                     | 541      |
| cause of death                        | 308      |
| food in                               | 61       |
| mellitus                              | 97       |
| Diagnosis, gastric analysis in        | 466      |
| G. I. disease                         | 56       |
| of appendiceal abscess                | 373      |
| of duodenal diverticula               | 20       |
| Diarrhea                              | 1        |
| classification of                     | 1        |
| functional                            | 623      |
| in ulcerative colitis                 | 66       |
| varieties                             | 3        |
| Diet, exclusive meat                  | 473, 732 |
| in constipation                       | 11       |
| in treatment of ulcerative colitis    | 82       |
| treatment by                          | 59       |
| Diets, gastrointestinal               | 476      |
| Digestion, in dogs without stomachs   | 599      |
| Diothane                              | 323      |
| Disease hepatic, liver function in    | 93       |
| urologic, G. I. manifestations        | 283      |
| visceral                              | 593      |
| Distention, effect of oxygen on       | 361      |
| in ulcerative colitis                 | 66       |
| Diverticula, duodenum in diabetes     | 17       |
| esophageal                            | 121      |
| of stomach                            | 116      |
| Diverticulitis, sigmoid               | 430      |
| treatment of                          | 322      |
| Diverticulosis, jejunal               | 507      |
| Diverticulum, duodenal                | 217, 436 |
| Meckel's                              | 188      |
| of esophagus                          | 642      |
| of jejunoileum                        | 646      |
| of stomach                            | 252      |
| Drip, method in ulcer                 | 733      |
| Drugs, and intestinal motility        | 668      |
| Duodenal extract, in treatment        | 189      |
| fluid, enzyme in                      | 224      |
| ulcer, traumatic                      | 135      |
| Duodenitis                            | 340      |
| Duodenum, buffer capacity of          | 288      |
| cysts of                              | 360      |
| diverticulum                          | 217      |
| drainage of                           | 663      |
| irritable                             | 173      |
| isolated                              | 285      |
| reaction in pancreatic fistula        | 298      |
| reaction without bile                 | 293      |
| reaction without pancreatic juice     | 295      |
| Dysentery                             | 213      |
| Dysentery and ulcerative colitis      | 408      |
| experimental                          | 16       |
| Dysphagia                             | 117      |
| of anemic women                       | 123      |
| Edema angioneurotic                   | 125      |
| Elimination diets                     | 306      |
| Emotions, in ulcerative colitis       | 651      |
| Enteritis, chronic cicatrizing        | 206      |
| Enterostomy, electrosurgical          | 630      |

|                                                     |          |                                             |                   |
|-----------------------------------------------------|----------|---------------------------------------------|-------------------|
| Enzymes, absorption from gut                        | 234      | Histidine, in peptic ulcer                  | 426               |
| blood serum                                         | 230      | Hunger, in hyperinsulinism                  | 564               |
| estimation of                                       | 224      | Hyperinsulinism, G. I. manifestations of    | 557               |
| in pancreatic juice                                 | 108      | Hyperparathyroidism                         | 566               |
| pancreatic in allergy                               | 422      | Hyperplasia, nodular, in ulcerative colitis | 78                |
| Esophagitis                                         | 124      | Hyperthyroidism                             | 97                |
| peptic                                              | 412      | Hypopharynx, anesthetization of             | 281               |
| treatment of                                        | 379      | Hysteria, dysphagia in                      | 125               |
| Esophagus                                           | 322, 391 | Icterus, hepatic                            | 346               |
| atony of                                            | 125      | Ileitis, distal                             | 724               |
| diseases of                                         | 412      | regional                                    | 126               |
| diverticulum of                                     | 642      | terminal                                    | 201, 213, 442     |
| rupture of                                          | 100      | Ileocolitis                                 | 586               |
| spasm of                                            | 125      | Impaction, fecal                            | 638               |
| surgery of                                          | 323      | Indigestion, nervous                        | 353               |
| Exercise, in diarrhea                               | 12       | Insulin-glucose therapy                     | 236               |
| Experimental biliary obstruction                    | 101      | Intestine, in diarrhea                      | 1                 |
| visceral disease                                    | 593      | small                                       | 395               |
| Feces, in ulcerative colitis                        | 67       | Intestine, stricture of                     | 323               |
| Fever, relapsing                                    | 100      | tuberculosis of                             | 209               |
| Fistula, gastroduodenal                             | 756      | Intussusception                             | 645               |
| gastrojejunal                                       | 673      | Iodoxyquinolin                              | 568               |
| pancreatic                                          | 650      | Jaundice                                    | 305               |
| pancreatic, experimental                            | 302      | chronic hemolytic                           | 26                |
| recto-urethral                                      | 744      | galactose tolerance in                      | 16                |
| Flora, oral bacterial                               | 275      | intrahepatic                                | 718               |
| Food allergy                                        | 178      | latent                                      | 412               |
| Foreign bodies in esophagus                         | 118      | painless                                    | 360               |
| Frei test                                           | 570      | and viosterol                               | 368               |
| Fruit juice, acid-base value                        | 242      | Jejunum, reaction in pancreatic fistula     | 298               |
| Function, hepatic                                   | 167      | Juices, digestive, dry                      | 33                |
| test, hepatic                                       | 93       | pancreatic                                  | 108               |
| Funduscopy                                          | 508, 641 | pancreatic, buffer capacity                 | 300               |
| Gall bladder                                        | 394      | Lactation, glycosuria in                    | 27                |
| in pregnancy                                        | 672      | lactosuria in                               | 27                |
| Gall stones                                         | 511      | Lactose, nutritive value of                 | 37                |
| Gastrectomy, evacuation after                       | 608      | Lead poisoning                              | 257               |
| Gastric analysis                                    | 402      | Lesions, hemorrhoidal                       | 631               |
| Gastric evacuation, after gastrectomy               | 608      | Lesions, gastric dysphagia in               | 125               |
| Gastritis, chronic                                  | 247      | organic in diarrhea                         | 5                 |
| diagnosis of                                        | 575      | Liver, amebic abscess of                    | 47                |
| Gastroenterostomy                                   | 434      | blood enzymes and                           | 233               |
| anterior                                            | 585      | changes, effect on carbohydrate metabolism  | 532               |
| Gastro-intestinal manifestations of urinary disease | 477      | Liver function                              | 93, 112, 167, 282 |
| Gastroscope, flexible                               | 656      | function test                               | 713, 716          |
| Gastrosocopy                                        | 280, 656 | hippuric acid test                          | 716               |
| Gelatine, in muscular dystrophy                     | 37       | infarction of                               | 508               |
| Giardiasis                                          | 350      | regeneration of                             | 105               |
| Globus hystericus                                   | 125      | Loewi's pupillary sign                      | 453               |
| Glucose-insulin therapy                             | 236      | Lymphadenitis, mesenteric                   | 356               |
| Glycosuria, in pregnancy                            | 27       | Lymphoma, hepatic                           | 96                |
| Grafts, omental                                     | 46       | Lymphopathia venerea                        | 570, 741          |
| Halstead sign                                       | 453      | Manganese retention                         | 37                |
| Headache, chronic                                   | 625      | Mayo-Robson sign                            | 453               |
| pituitary                                           | 37       | Meat, exclusive diet of                     | 473, 732          |
| Healing, in ulcerative colitis                      | 78       | Megaloclon                                  | 507               |
| Heart disease, insulin-glucose therapy in           | 236      | Meniere's disease                           | 243               |
| Hemorrhage, in peptic ulcer                         | 255      | Metabolism, calcium                         | 615               |
| suprarenal                                          | 504      | carbohydrate, in liver changes              | 532               |
| Hepatitis                                           | 719      | and pancreas                                | 413               |
| acute                                               | 93       | Microscopy, of gastric lavage               | 214               |
| chronic                                             | 94       | Migraine                                    | 397               |
| in Brucella infection                               | 20       | state                                       | 401               |
| Hepatomegaly                                        | 95       | Milk                                        | 113               |
| Hepatoptosis                                        | 161      | consumption of                              | 417               |
| Heredity, in G. I. lesions                          | 724      | evaporated                                  | 114               |
| Hernia, diaphragmatic                               | 310      | Mineral deficiency                          | 730               |
| esophageal orifice                                  | 120      | Motility of intestinal segments             | 668               |
| left duodenal                                       | 569      | small bowel                                 | 725               |
| Hernia, hiatus                                      | 311      | stomach of                                  | 671               |
| Herpes, dysphagia in                                | 125      |                                             |                   |



|                                        |          |                                         |               |
|----------------------------------------|----------|-----------------------------------------|---------------|
| Mouth                                  | 391      | Sign, Halstead                          | 453           |
| bacterial flora                        | 275      | Mayo-Robson                             | 453           |
| Mucin, gastric                         | 20       | Sodium ricinoleate                      | 626           |
| Mutations bacterial                    | 111      | Solution, Lugol's                       | 592           |
| Neoplasms, of esophagus                | 119      | Spinal cord disease, and abdominal pain | 520           |
| hepatic                                | 95       | Stenosis, mycotic, of esophagus         | 125           |
| Neurological changes                   | 37       | of esophagus                            | 120           |
| Noma                                   | 698      | pyloric                                 | 430, 613      |
| Obesity, and hyperinsulinism           | 564      | "Strokes," unrecognized                 | 90            |
| treatment of                           | 116      | Surgery, in ulcerative colitis          | 87            |
| Obstruction, biliary, experimental     | 101, 174 | Stomach, bleeding from                  | 62            |
| intestinal                             | 323      | cascade                                 | 38            |
| intestinal experimental                | 613, 26  | delayed emptying                        | 217           |
| Oesophagitis, see Esophagitis          |          | diverticulum of                         | 252, 697      |
| Oil, peppermint                        | 251      | effect of removal                       | 599           |
| and gastric emptying                   | 526      | emptying time                           | 671           |
| Oxygen, effect on distention           | 361      | lavage microscopy                       | 214           |
| Pain, abdominal                        | 260      | reaction in pancreatic fistula          | 298           |
| in brain disease                       | 506      | resection of                            | 706           |
| in spinal cord disease                 | 520      | thoracic                                | 124           |
| in peptic ulcers                       | 283      | Symptoms, urogenital                    | 758           |
| Pancreas                               | 395      | Syndrome, Plummer-Vinson                | 123           |
| carcinoma of                           | 248      | "retroperitoneal"                       | 478           |
| and metabolism                         | 413      | Syphilis, of esophagus                  | 124           |
| necrosis of                            | 271      | Test, blood sedimentation               | 613           |
| subtotal resection of                  | 617      | Frei                                    | 570           |
| Pancreatic juice, buffer capacity      | 300      | hippuric acid                           | 716           |
| Pancreatitis, acute                    | 449, 697 | meal, in diagnosis                      | 173           |
| surgery of                             | 585      | Takata-Ara                              | 713           |
| Paralysis, of esophagus                | 122      | Weldmann in liver disease               | 14            |
| Pectinosis                             | 574      | Tests, intradermal                      | 410           |
| Pellagra, liver treatment of           | 378      | Theory, "gradient" of diarrhea          | 9             |
| treatment of                           | 308      | Therapy, antiretentional                | 243           |
| Peppermint oil                         | 251      | B. Coli vaccine                         | 621           |
| Peptic ulcer, cancer and               | 526      | insulin-glucose                         | 236, 447      |
| etiology of                            | 333      | vaccine, in ulcerative colitis          | 65            |
| pancreatic fistula in                  | 302      | Tract, biliary, treatment               | 44            |
| perforated                             | 195      | Treatment, of allergy by enzymes        | 422           |
| post-operative                         | 52       | of amebiasis                            | 568           |
| treatment                              | 411      | of biliary tract                        | 44            |
| Perfection of stomach, neurogenic      | 20       | cascade stomach                         | 41            |
| "Peristaltin"                          | 669      | of diarrhea                             | 5, 12         |
| Peritonitis, treatment of              | 52       | Treatment, of duodenal diverticula      | 20            |
| Phenolphthalein                        | 721      | of esophagitis                          | 379           |
| Physiology, of constipation            | 8        | of giardiasis                           | 353           |
| Physostigmine                          | 669      | of hemorrhoids                          | 632           |
| Pigmentation biliary                   | 107      | of migraine                             | 398           |
| Pituitrin                              | 669      | serum in colitis                        | 410           |
| Pleurodynia, epidemic                  | 46       | ulcer                                   | 736           |
| Polyposis, gastric                     | 386      | ulcerative colitis                      | 82            |
| Pregnancy, glycosuria in               | 27       | Tuberculosis, of esophagus              | 124           |
| lactosuria in                          | 27       | intestinal                              | 209, 126      |
| Proctoscopy, ulcerative colitis in     | 68       | Tubes, stomach and duodenal             | 498           |
| Protein, diet in                       | 46       | Tumors, argentaffin                     | 598           |
| Pruritis, ani                          | 53       | of esophagus                            | 123           |
| Psychotherapy, ulcerative colitis in   | 653      | of small intestine                      | 51            |
| Rectum, cancer of                      | 586      | Ulcer, duodenal diagnosis and treatment | 667           |
| treatment in ulcerative colitis        | 87       | duodenal, traumatic                     | 135           |
| varicose disease of                    | 327      | gastric                                 | 271           |
| Reflex, defecation                     | 11       | gastrojejunal                           | 584           |
| Resection, gastric for ulcer           | 640      | jejunal, perforated                     | 510           |
| Rings, "Liesegang"                     | 515      | post-operative                          | 673           |
| Roentgenography, in ulcerative colitis | 71       | peptic                                  | 360, 393      |
| Roentgenology, of dysphagia            | 117      | bleeding                                | 431           |
| Saponin                                | 723      | complications of                        | 100           |
| Sarcoma, diverticular                  | 185      | drip treatment                          | 733           |
| of pancreas                            | 435      | esophagus of                            | 124           |
| Secretion, gastric, autoregulation of  | 527      | etiology of                             | 333, 437, 683 |
| Serum sickness, dysphagia in           | 125      | experimental                            | 302, 586      |
| Sigmoid, trauma                        | 678      | hemorrhage in                           | 255           |
|                                        |          | histidine in                            | 426           |
|                                        |          | polycythemia and                        | 584           |

|                                               |     |                                      |     |
|-----------------------------------------------|-----|--------------------------------------|-----|
| spasm in                                      | 235 | Vertigo, toxic                       | 623 |
| surgery of                                    | 648 | Vioosterol, and bleeding in jaundice | 368 |
| treatment                                     | 736 | Viscera, disease of                  | 593 |
| treatment after                               | 421 | Vitamin B (1), and diabetes          | 541 |
| treatment by mucin                            | 421 | in large bowel tonus                 | 618 |
| Ulceration, in ulcerative colitis             | 74  | Vitamin B, in yeast                  | 378 |
| Undulant fever                                | 307 | Vitamins, popular stampede           | 128 |
| Urinary tract disease                         | 477 |                                      |     |
| Urogenital symptoms                           | 758 | Weldmann test in liver disease       | 14  |
| Urticaria, dysphagia in                       | 125 |                                      |     |
|                                               |     | X-ray, appendiceal abscess           | 373 |
| Vaccine, in ulcerative colitis                | 65  |                                      |     |
| Vaccine therapy in ulcerative colitis, part 2 | 139 | Zinz peroxide                        | 321 |
| Varix, esophageal                             | 123 |                                      |     |

